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Multi-Component Regio- and Diastereoselective Cobalt-catalyzed Hydrovinylation/Allylboration Reaction Sequence

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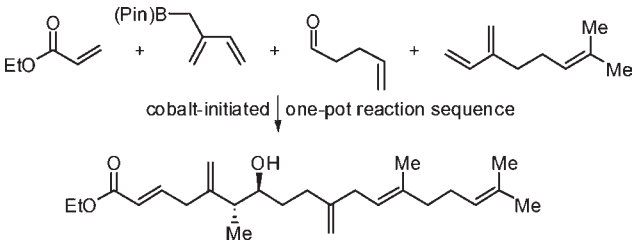
ABSTRACT

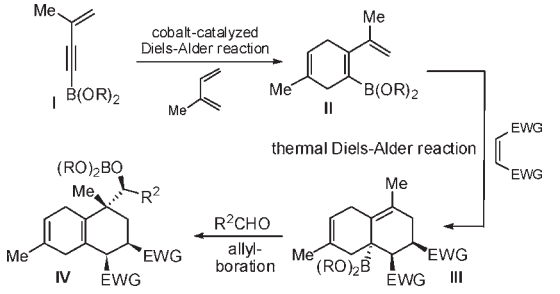


The combination of a regioselective cobalt-catalyzed 1,4-hydrovinylation and the diastereoselective allylboronation reaction leads to a wide scope of functionalized hydroxydienyl esters in a one-pot reaction in excellent yields. With catalytic amounts of base, these products are easily converted either into α,β,γ,δ-unsaturated hydroxyl esters or complex tetrasubstituted tetrahydropyrans in chemo- and diastereoselective fashions. In addition, a high-yielding four-component one-pot reaction involving an acrylate, two different and unsymmetrical 1,3-dienes, and an unsaturated aldehyde is presented.

The combination of highly selective carbon−carbon bond formation processes in atom economic multicomponent reactions is state-of-the-art chemistry. Applications realizing chemo-, regio- and diastereoselective carbon−carbon bond formations while modifying the reactivity of a functional substructure over the course of the reaction sequence are quite rare.[1] An example for a continuously changed functionality of a substructure over the course of a reaction sequence from alkynyl- (**I**) over dienyl- (**II**) and allyl-boron (**III**) toward a boronic ester (**IV**) is given in Scheme 1.[1c]

A versatile method for atom economic carbon−carbon bond formations are transition metal-catalyzed 1,2- and 1,4-hydrovinylation reactions.[2,3]

Scheme 1. Four-component Synthesis of Bicyclic Product **IV**



We envisaged that the cobalt-catalyzed 1,4-hydrovinylation of 1,3-butadiene derivatives with alkenes of different electron demand could realize a similar transformation based on the excellent regioselectivity and functional group

(1) For recent reviews on transition metal- and organo-catalyzed multicomponent reactions, see: (a) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539. (b) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857. For a recent example of a multicomponent reaction initiated by cobalt-catalysis, see:(c) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251.

(2) For selected recent references on transition metal-catalyzed hydrovinylation reactions, see: (a) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (b) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000. (c) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (d) Lassauque, N.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 3133. (e) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414.

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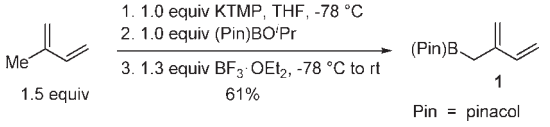
tolerance observed in these reactions.[3] The versatility of this transformation has been demonstrated in the past decade in applications for the synthesis of polycarbonyl derivatives and natural products.[4,5]

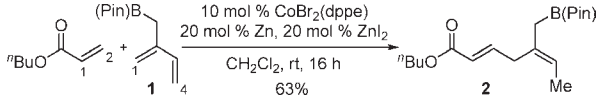
Nevertheless, the 1,3-butadiene derivatives used so far remained mainly alkyl-substituted. To accomplish a multicomponent reaction sequence, isoprene was converted into isoprenylpinacol boronic ester **1** via deprotonation with in situ generated potassium tetramethylpiperidine (KTMP) following a procedure by Brown.[6] Thereby, product **1** could be obtained on gram scale in pure form by flash chromatography (Scheme 2).

Scheme 2. Synthesis of Isoprenylpinacol Boronic Ester **1**



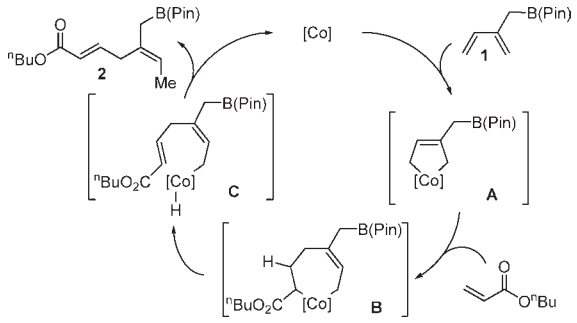
The boron-functionalized isoprene **1** was then reacted with *n*-butyl acrylate using the well-established and simple catalyst system comprising $CoBr_2$(dppe), zinc, and zinc iodide in dichloromethane.[7] The crotylpinacol boronic ester **2** could be isolated as a single stereoisomer with complete regioselectivity regarding both components (Scheme 3).[8]

Scheme 3. 1,4-Hydrovinylation of **1** with Butyl Acrylate



The carbon−carbon bond formation takes place exclusively at C2 of the acrylate and C1 of the butadiene derivative **1**. This result is notably pleasant compared to the conversion of isoprene with butyl acrylate, which led to a mixture of regioisomers.[9] The outcome of this transformation can be rationalized by the proposed mechanism (Scheme 4).

Scheme 4. Proposed Mechanism of the Cobalt-catalyzed 1,4-Hydrovinylation[a]



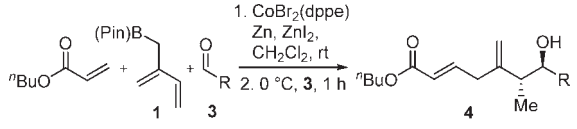
[a] Ligands are omitted for clarity.

After π-complex formation of the cobalt(I) species with the electron-rich diene **1**, oxidative [1 + 4] cycloaddition leads to the cobaltacyclopentene intermediate **A** defining the (5*Z*)-configuration of the product **2**. The acrylate coordination and regioselective insertion leads to the cobaltacycloheptene intermediate **B**. A subsequent β-hydride elimination generates the (2*E*)-configuration in intermediate **C** selectively. The catalytic cycle is then completed by reductive elimination for the liberation of **2** and regeneration of the catalytically active cobalt species.

As the boronic ester **2** appeared to decompose on silica gel in situ, allylboration of aldehydes **3** was investigated. Accordingly, a cobalt-catalyzed 1,4-hydrovinylation/allylboration (HVAB) one-pot reaction sequence was developed (Scheme 5).

A wide range of aliphatic, aromatic, heteroaromatic and vinylic aldehydes could be introduced generating the corresponding products of type **4** in excellent yields and exclusive *anti*-diastereoselectivity. The results of these three-component reactions are summarized in Table 1.

Scheme 5. Cobalt-catalyzed HVAB Reaction Sequence for the Regio- and Diastereoselective Synthesis of Bifunctionalized 1,4-Dienes **4**



Notably, the aldehyde residues do not seem to have a significant influence on the excellent yields achieved over two formal steps. The *anti*-selectivity of the sequence can

(3) (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (b) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (b) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (c) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (d) Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Thieme: Stuttgart, 2001; Vol. 1, p 439. (e) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (f) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (g) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(4) (a) Hilt, G. *Synlett* **2011**, 1654. (b) Kersten, L.; Roesner, S.; Hilt, G. *Org. Lett.* **2010**, *12*, 4920. (c) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (d) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321.

(5) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395.

(6) Brown, H. C.; Randad, R. S. *Tetrahedron* **1990**, *46*, 4463.

(7) dppe = 1,2-bis(diphenylphosphino)ethane.

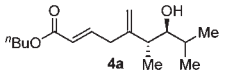
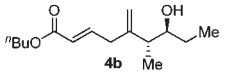
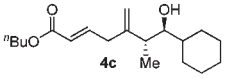
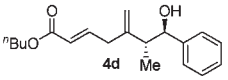
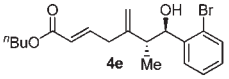
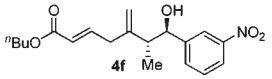
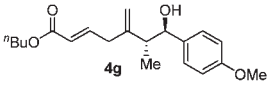
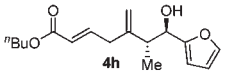
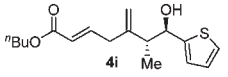
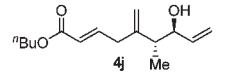
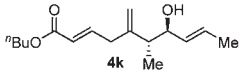
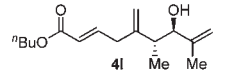
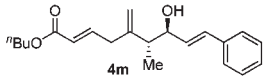
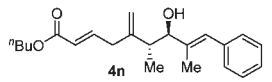
(8) For cobalt-catalyzed reactions involving borylated partners, see: (a) Geny, A.; Leboeuf, D.; Rouquié, G.; Vollhardt, K. P. C.; Malacria, M.; Gandon, V.; Aubert, C. *Chem.—Eur. J.* **2007**, *13*, 5408. (b) Leboeuf, D.; Iannazzo, L.; Geny, A.; Malacria, M.; Vollhardt, K. P. C.; Aubert, C.; Gandon, V. *Chem.—Eur. J.* **2010**, *16*, 8904. (c) Hilt, G.; Erver, F.; Harms, K. *Org. Lett.* **2011**, *13*, 304.

(9) Hilt, G.; Lüers, S.; Schmidt, F. *Synthesis* **2004**, 634.

be rationalized by simple diastereoselectivity based on the Zimmermann–Traxler model for allylboration reactions.

Treatment of **4a** with 50 mol % sodium hydride at 0 °C led to a 1:1 mixture of **5a** (two diastereoisomers) and **6a**. This led to the conclusion that the esters of type **4** have two positions with similar acidity.

Table 1. Results of the Cobalt-catalyzed HVAB Reaction of *n*-Butyl Acrylate, Boronic Ester **1** and Aldehyde **3**[a]

no.	main product **4**[b]	dr[c]	yield[d]
1	 **4a**	95:5	99%
2	 **4b**	95:5	75%
3	 **4c**	95:5	77%
4	 **4d**	93:7	82%
5	 **4e**	94:6	95%
6	 **4f**	94:6	96%
7	 **4g**	90:10	74%
8	 **4h**	93:7	88%
9	 **4i**	96:4	99%
10	 **4j**	95:5	84%
11	 **4k**	95:5	98%
12	 **4l**	95:5	81%
13	 **4m**	95:5	90%
14	 **4n**	93:7	87%

[a] $CoBr_2$(dppe) (10 mol %), zinc dust (20 mol %), zinc iodide (20 mol %), *n*-butyl acrylate (1.1 equiv) and isoprenylpinacol boronic ester **1** (1.1 equiv), 16 h then 0 °C, aldehyde **3** (1.0 equiv), 1 h then triethanolamine (1.1 equiv), 1 h, rt. [b] Only one enantiomer is shown. [c] The dr was determined by ^{1}H NMR spectroscopy. [d] Isolated yield.

The choice of base addressed a reactivity difference between the two positions to produce the corresponding isomers chemo- and diastereoselectively. Utilizing catalytic

Scheme 6. Base-initiated Follow-up Reactions of **4**

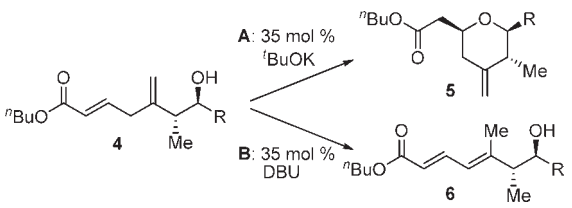
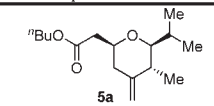
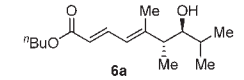
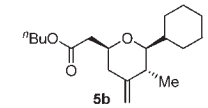
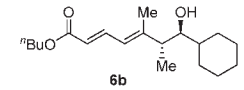
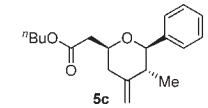
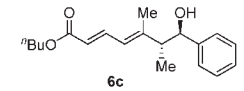
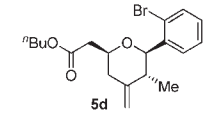
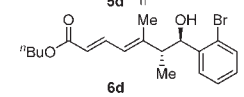
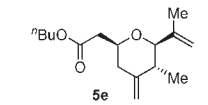
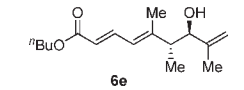
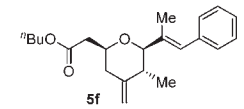
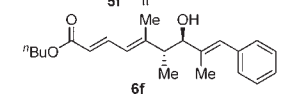


Table 2. Results for the Base-initiated Michael Addition[a] and Isomerization of Hydroxydienyl Esters **4**[b]

no.	main products **5** or **6**[c]	dr or *E*/*Z*[d]	yield[e]
1	 **5a**	90:10	80%[a]
2	 **6a**	91:9	83%[b]
3	 **5b**	95:5	85%[a]
4	 **6b**	80:20	99%[b]
5	 **5c**	98:2	75%[a]
6	 **6c**	81:19	99%[b]
7	 **5d**	95:5	60%[a]
8	 **6d**	93:7	61%[b]
9	 **5e**	96:4	63%[a]
10	 **6e**	81:19	85%[b]
11	 **5f**	95:5	70%[a]
12	 **6f**	81:19	73%[b]

[a] Method **A**: Potassium *t*-butoxide (35 mol %), CH_2Cl_2 (0.05 M), 0 °C to rt, 16 h. [b] Method **B**: DBU (35 mol %), CH_2Cl_2 (0.15 M), rt, 16 h. [c] Only one enantiomer is shown. [d] The dr and *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [e] Isolated yield.

amounts of potassium *t*-butoxide led to the exclusive formation of tetrasubstituted tetrahydropyrans (THPs) **5** by a Michael addition, generating an additional stereogenic center diastereoselectively.[10] Alternatively, DBU enables the selective formation of the α,β,γ,δ-unsaturated esters of type **6** mainly as the *E*,*E*-isomer (Scheme 6).[11]

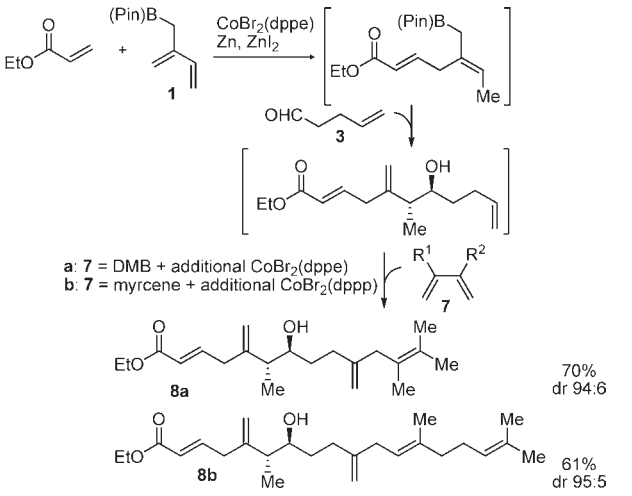
In a proof-of-principle investigation, six hydroxyl esters of type **4** were chosen for conversion to their corresponding THPs or to the conjugated esters (Table 2).

In all reactions, good to excellent yields for the products of type **5** and **6** were obtained. Accordingly, both reaction pathways allow a very flexible approach toward both types of products. The observed exclusive chemoselectivity and base affinity of the isomerization reactions is astounding. In fact, both bases are known to initiate the intramolecular Michael addition as well as the isomerization reaction to conjugated esters.[12,13]

Last but not least, the combination of a cobalt-catalyzed 1,4-hydrovinylation of an acrylate with **1** toward a linear product, with an allylboration using an unsaturated aldehyde **3** and then with a cobalt-catalyzed 1,4-hydrovinylation applying another 1,3-diene (**7**) toward a branched product, could be realized. This four-component one-pot reaction sequence was performed applying 2,3-dimethylbuta-1,3-diene (DMB) or myrcene as 1,3-diene at the end of the reaction sequence (Scheme 7). In the case of the reaction with myrcene, the catalyst precursor $CoBr_2$(dppp) was added to the reaction mixture based on the higher C1/C4 selectivity of the 1,4-hydrovinylation with 2-substituted buta-1,3-dienes.[5,14]

In this sequence, three carbon−carbon bonds were formed, providing the products **8a** and **8b** with complete regio- and diastereoselectivity in every single transformation. Both products were obtained in excellent yields over three formal steps without isolation of the intermediates in a one-pot procedure after a single column chromatography. Moreover, for the formation of **8b**, both types of cobalt-catalyzed 1,4-hydrovinylation modes, linear and branched, were applied.[3b,c]

Scheme 7. Multi-component One-pot Reaction via Two Cobalt-catalyzed 1,4-Hydrovinylations and Allylboration



The unique combination of both regioselective cobalt-catalyzed carbon-bond forming processes and an intermediate allylboration of an unsaturated aldehyde provided this unprecedented access to a complex acyclic isoprenoide-type product **8b** in a single relatively high yielding one-pot process.

In conclusion, we have demonstrated that the cobalt-catalyzed 1,4-hydrovinylation of acrylates with isoprenylpinacol boronic ester **1** and subsequent allylboration of aldehydes represents a powerful tool in the regio- and diastereoselective generation of increasingly complex organic building blocks starting from readily available substrates. Furthermore, a base-initiated isomerization was developed to gain access to α,β,γ,δ-unsaturated esters and a diastereoselective Michael addition led to tetrasubstituted tetrahydropyrans.

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Supporting Information Available. Experimental procedures and full characterization of the compounds obtained in pure form. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) dppp = 1,2-bis(diphenylphosphino)propane.