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Novel Isomerically Pure Tetrasubstituted Allylboronates: Stereocontrolled Synthesis of α-Exomethylene γ-Lactones as Aldol-Like Adducts with a Stereogenic Quaternary Carbon Center

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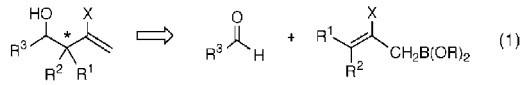
The stereoselective construction of chiral quaternary carbon centers is one of the most difficult transformations in organic synthesis.[1] There are very few general methods available for realizing this task in a highly diastereo- and enantiocontrolled fashion.[2] Aldol-based methodologies are generally not applicable due to the lack of *E/Z* selectivity in the enolization of α,α-disubstituted carbonyl compounds.[3] Similarly, with respect to stereogenic quaternary carbons (eq 1), a significant limitation of allylboration methodology[4] resides in the preparation of the required 3,3-disubstituted allylboronates (R^1, R^2 = alkyl or aryl) with high *E/Z* isomeric purity.



(1)

These reagents cannot be synthesized readily from reactive allylmetal species and borate esters.[5] One alternate route features the reaction of configurationally stable alkenylmetal reagents with halomethylboronates.[6] A caveat to this approach, however, is the need for a very reactive metal (e.g., Li, Mg) and the consequent lack of functional group compatibility. For instance, although alkenylcopper reagents are easily accessed from alkynes, they need to be transmetalated to lithium, via the corresponding iodide, for efficient trapping with a chloromethylboronic ester to provide 3,3-disubstituted allylboronates.[7] Herein, we report a direct entry into a new class of tetrasubstituted 2-alkoxycarbonyl allylboronates,[8] generated as pure isomers in a single operation by the carbocupration of readily available alkynoate esters. Subsequent addition to aldehydes affords α-methylene-γ-lactones as aldol-like adducts with a stereogenic, quaternary β-carbon center in very high diastereo- and enantioselectivity. These lactones are part of a family of biologically important compounds with significant interest in organic synthesis.[9]

The conjugate addition of organocopper reagents to acetylenic esters is a prime method to access isomerically pure, trisubstituted α,β-unsaturated esters.[10] Unfortunately, extensions toward synthesizing tetrasubstituted alkenes[11] have been hampered by the low reactivity of 1-alkoxycarbonyl vinylcopper(I) intermediate **3** and its tendency to isomerize via a copper allenoate (**4**) at temperatures above −30 °C (Figure 1).[12] Yet we anticipated that halomethylboronates (**6**−**8**) could be sufficiently reactive, under optimal conditions, to trap **3** with no loss of stereochemical integrity and afford tetrasubstituted allylboronates **9** with overall *cis*-addition.

Our first investigations focused on optimizing conditions for the preparation of allylboronate **9a** using ethyl 2-butynoate and Me_2CuLi (Table 1). Initially, it was clear that electrophiles **6** and **7** lacked the requisite reactivity to trap the sluggish intermediate **3**. Satisfactorily, the more potent iodo analogue (**8**)[13] was found to be effective, although poor yield and selectivity were observed in

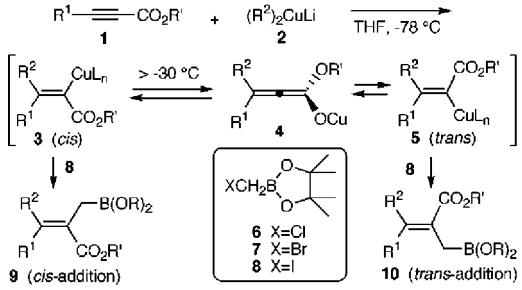


Figure 1. Formation of 2-alkoxycarbonyl allylboronates by tandem carbocupration of alkynoate esters/electrophilic trapping with **8**.

Table 1. Preparation of Isomerically Pure Tetrasubstituted Allylboronates **9** from *cis*-Addition between **1** and **2** in THF[a]

entry	R^1	R^2	R′	additive	product	yield[b] (%)	ratio[c] **9**:**10**
1	Et	Me	Et	none	**9a** (*Z*)	43	1.4:1
2	Et	Me	Et	HMPA (1 equiv)	**9a**	>95	4:1
3	Et	Me	Et	HMPA (3 equiv)	**9a**	>95	12:1
4	Et	Me	Et	HMPA (9 equiv)	**9a**	>95	>20:1
5	Bu	Me	Me	DMPU (1:1)	**9b** (*Z*)	85	>20:1
6	Me	Bu	Et	HMPA (9 equiv)	**9c** (*E*)	>95	>20:1
7	Me	Me	Et	HMPA (9 equiv)	**9d**	>95	-
8	H	Me	Me	HMPA (9 equiv)	**9e** (*E*)	>95	>20:1
9	Me	*s*Bu	Et	HMPA (9 equiv)	**9f** (*E*)	70[d]	13:1
10[e]	Me	*i*Bu	Et	HMPA (9 equiv)	**9g** (*E*)	45[d]	>20:1
11[e]	Me	allyl	Me	HMPA (9 equiv)	**9h** (*E*)	60[d]	19:1
12[f]	$POCH_2$	Me	Me	HMPA (9 equiv)	**9i** (*Z*)	60[d]	>20:1

[a] Allylboronates **9** were prepared as described in the text and Supporting Information. [b] Unoptimized yields of crude products. [c] Ratio of *cis*-addition to *trans*-addition products **9**:**10** (determined by ^1H NMR). [d] Purified by flash chromatography. [e] Made from Grignard reagents R^2MgCl and CuBr. [f] P = *t*-$BuPh_2Si$.

THF alone as solvent (entry 1). As shown with entries 2−4, small amounts of HMPA had a huge impact on the reaction. Not only were the yields improved, but *cis*-addition products were obtained almost exclusively with nine equiv. of HMPA.[14] The use of DMPU as cosolvent was also effective but yields were generally lower. Cuprates formed from Grignard reagents work equally well. Through using the *crucial combination of HMPA as additive and iodomethylpinacol boronate as the electrophile*, several tetrasubstituted allylboronates **9** were generated in very high *cis*-addition selectivity. As shown with **9b** and **9c** (entries 5−6), permutation of respective alkyne and cuprate R^1 and R^2 groups allows isomeric allylboronates to be made independently. Functionalized acetylenic esters can also serve as effective precursors. In this respect, allylboronate **9i** bears a versatile, masked formyl group at the R^1 position (entry 12).

A small excess (1.5 equiv) of the crude allylboronates **9** were treated immediately with various aliphatic and aromatic aldehydes (Table 2). While the reactions are rather slow, they are operationally simple and even those with *p*-MeO-benzaldehyde (a notoriously

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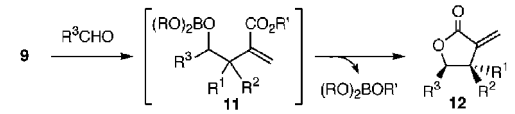
Table 2. Stereocontrolled Synthesis of γ-Lactones **12**



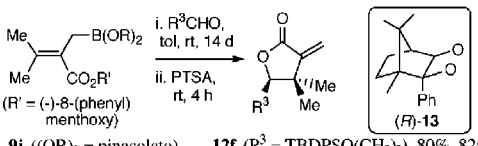
entry	boronate (R^1,R^2)	aldehyde (R^3)	conditions[a]	product	yield (%)[b]	dr[c]
1	**9a** (Et, Me)	C_6H_5	A	**12a**	89	>20:1
2	**9a** (Et, Me)	4-MeO−C_6H_4	B	**12b**	70	19:1
3	**9a** (Et, Me)	4-MeO−C_6H_4	C	**12b**	55	20:1
4	**9a** (Et, Me)	4-NO_2−C_6H_4	B	**12c**	81	>20:1
5	**9b** (Bu, Me)	4-NO_2−C_6H_4	B	**12d**	76	>20:1
6	**9c** (Me, Bu)	4-NO_2−C_6H_4	D	**12e**	67	>20:1
7[d]	**9d** (Me, Me)	$PO(CH_2)_2$	E	**12f**	75	
8	**9a** (Et, Me)	C_9H_{19}	A	**12g**	68	18:1
9	**9e** (H, Me)	C_6H_5	B	**12h**	60	>20:1
10	**9f** (Me, *s*Bu)	4-NO_2−C_6H_4	A	**12i**	26	15:1[e]
11	**9g** (Me, *i*Bu)	4-MeO−C_6H_4	C	**12j**	65	>20:1
12	**9h** (Me, allyl)	4-MeO−C_6H_4	C	**12k**	48	*f*
13[d]	**9i** ($POCH_2$, Me)	4-NO_2−C_6H_4	B	**12l**	75	>20:1

[a] Reaction scale: approximately 1 mmol. Methods. A: toluene, rt, >12 d; B: toluene, 80 °C, 16−120 h; C: toluene, 110 °C, 16−24 h; D: CH_2Cl_2, 40 °C, 48 h; E: neat, rt, >12 d. [b] Unoptimized yields of pure products isolated after flash chromatography (for **12j** and **12l**) and Kugelrohr distillation (**12a**−**i**,**k**). [c] Determined by ^{1}H NMR or HPLC. [d] P = *t*-$BuPh_2Si$. [e] 1:1 mixture of epimers at the *s*-butyl side chain center. [f] The [3,3] rearrangement product was isolated.

unreactive substrate) are completed within 24 h at elevated temperature with no apparent loss of stereoselectivity (see entries 3,11). Most examples provided good yields of pure α-methylene-β-disubstituted-γ-lactones **12** after distillation. The latter are formed in situ from the putative initial addition product **11**.[15] In all cases a single or highly predominant diastereomer (with syn R^2 and R^3 substituents) was obtained. *The process appears to be stereospecific:* the geometry of isomeric allylboronates **9b** and **9c** was transferred respectively into diastereomers **12d**/**12e** with no apparent loss of selectivity (entries 5−6). This latter pair of examples highlights the power of this approach at affording excellent diastereocontrol in the formation of β-hydroxy quaternary carbon centers.

The relative stereochemistry observed in these allylborations was confirmed with selective nOe experiments on epimeric lactones **12d** and **12e**.[16] The excellent level of diastereoselection is consistent with the expected Zimmerman−Traxler chairlike transition structure with R^3 in a pseudoequatorial orientation.

Preliminary results with chiral 3,3-dimethyl allylboronates showed that enantiopure lactones **12** can be obtained using a convenient, dual traceless auxiliary approach whereby chiral educts on the alcohol and the boronate are cleaved simultaneously in the product forming step (eq 2). While the phenylmenthyl ester in **9j** and **9l**−**m** is present from **1**, the chiral dioxyboronate unit **13**[17] can be installed via facile transesterification of the corresponding diisopropoxy allylboronates.[18] By making use of allylboronate **9m** featuring a matched combination of chiral inducers, high e.e.'s were obtained with representative aldehydes,[19] thereby opening up a promising enantioselective approach to the construction of stereogenic quaternary carbon centers.



(2)

9j ((OR)$_2$ = pinacolato) **12f** (R^3 = TBDPSO(CH_2)$_2$), 80%, 82% e.e.
9k (R' = Et, (OR)$_2$ = (*R*)-**13**) **12m** (R^3 = C_9H_{19}), 60% e.e.
9l ((OR)$_2$ = (*S*)-**13**) **12m** (R^3 = C_9H_{19}), 10% e.e.
9m ((OR)$_2$ = (*R*)-**13**) **12m** (R^3 = C_9H_{19}), 75%, 98% e.e.
9m ((OR)$_2$ = (*R*)-**13**) **12n** (R^3 = Ph), 55%, >95% e.e.

In summary, by overcoming the inherent isomerization tendency and low reactivity of 1-alkoxycarbonyl vinylcopper(I) intermediates, we have developed the first direct and general entry into isomerically pure 3,3-disubstituted 2-alkoxycarbonyl allylboronates. These allylboronates add onto aldehydes, in a highly diastereo- and enantioselective manner, to afford α-exomethylene γ-lactones with a stereogenic quaternary β-carbon center. These adducts are not attainable using standard aldol-based methodologies.

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Supporting Information Available: Experimental details, characterization data (IR, NMR, MS), and spectral reproductions for all allylboronates and lactones (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This result suggests that the additive stabilizes vinylcopper intermediate **3**, thereby allowing **8** to trap it prior to isomerization to **5** (Figure 1) and hence avoiding erosion of selectivity via formation of **10**. For a brief discussion of solvent effects on the stability of 1-alkoxycarbonyl vinylcuprate intermediates, see: Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265−6268.
(15) In rare instances where lactonization is incomplete (e.g, entry 9), it was easily promoted under mild acid catalysis (cat. PTSA, CH_2Cl_2, rt).
(16) See Supporting Information for full details.
(17) Herold, T.; Schrott, U.; Hoffmann, R. W. *Chem. Ber.* **1981**, *114*, 359−374.
(18) Made from the trapping of **3** with $ICH_2B(O\text{-}i\text{-}Pr)_2$.
(19) The ee's were determined by chiral HPLC (Chiralpak AD-RH or Chiralcel OD, Daicel).[16] The sense of induction has not yet been assigned.

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