Ligand-controlled diastereodivergent, enantio- and regioselective copper-catalyzed hydroxyalkylboration of 1,3-dienes with ketones†

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A copper-catalyzed three-component coupling of 1,3-dienes, bis(pinacolato)diboron, and ketones allows for the chemo-, regio-, diastereo- and enantioselective assembly of densely functionalized tertiary homoallylic alcohols. The relative configuration of the vicinal stereocenters is controlled by the chiral ligand employed. Subsequent transformations illustrate the versatility of these valuable chiral building blocks.

Introduction

The enantioselective synthesis of tertiary homoallylic alcohols continues to attract attention as these are highly useful intermediates in complex molecule synthesis and for medicinal chemistry. An established way to access that motif is by ketone allylation where enantiofacial discrimination and low reactivity are the key challenges compared to aldehydes as electrophiles. Many methods are based on preformed allylmetal reagents. An alternative to these nucleophiles is their in situ formation by hydrometalation of 1,3-dienes and allenes, and examples of transition-metal-catalyzed reductive couplings with ketones were recently achieved. A powerful variation of this approach is the borylmetalation of 1,3-dienes in the presence of a carbon electrophile. These and related stereoselective borylative coupling reactions of other π-systems form a carbon–boron and a carbon–carbon bond in a single operation. However, reactions involving ketones as electrophiles are scarce.† The best of our knowledge, there are only three examples of the preparation of tertiary homoallylic alcohols by the borylative coupling strategy. Morken and co-workers reported a nickel-catalyzed three-component coupling of 1,3-dienes, bis(pinacolato)diboron, and ketones in racemic fashion (Scheme 1, top). The reaction outcome was dependent on the substitution pattern of the 1,3-diene; (E)-penta-1,3-diene converted into 4,3-hydroxyalkylboration products while isoprene (one example) afforded the 4,1-hydroxyalkylboration product. Starting from allenes as the precursor of the allylic nucleophiles, Hoveyda and co-workers realized enantioselective borylative couplings with carbonyl compounds with syn selectivity but enantiocontrol was lower for ketones than for aldehydes (Scheme 1, middle). Low enantioselectivity was found by Tian and Tao in an...

Scheme 1 Transition-metal-catalyzed intermolecular borylative coupling reactions of ketones for the construction of tertiary homoallylic alcohols. cod = cycloocta-1,5-diene, pin = pinacolato.
intramolecular borylative cyclization of allenes tethered to cyclohexanediones (not shown). Hence, there is a demand for the development of new enantioselective borylative coupling reactions of π-systems and ketones to access chiral tertiary homoallylic alcohols. We disclose here such a copper-catalyzed three-component reaction with 1,3-dienes as the allylic coupling partner where the diastereoselectivity is determined by the ligand (Scheme 1, bottom).}

Results and discussion

For optimization, the three-component reaction of acetophenone (1a), isoprene (2a), and B2(pin)2 was chosen as the model reaction. The ligand effects are summarized in Table 1. In general, the reaction catalyzed by CuCl and phosphoramidite ligands afforded anti-4aa as the major diastereomer after oxidative degradation of the carbon–boron bond (see the ESI† for the complete set of data). As an example, anti-4aa formed in decent yield and with moderate stereoselectivity at room temperature in the presence of CuCl/L1 and NaOtBu (entry 1). Further optimization of the copper source, solvent, and temperature led to a system which afforded the tertiary homoallylic alcohol anti-4aa as the major diastereomer in 94% NMR yield and with 90% ee (entries 2–4). In contrast to phosphoramidite ligands, bisphosphine ligands commonly used in copper catalysis such as L2 to L12 furnished syn-4aa as the major diastereomer at room temperature (entries 5–17), and commercially available josiphos derivative L9 was found to be optimal (entry 12). Lowering of reaction temperature from room temperature to –20 °C increased the enantiomeric excess and diastereoselectivity significantly but was detrimental to the yield (entry 13). Finally, high yield (98% NMR yield) and stereoselectivity (93% ee and d.r. = 87 : 13 in favor of syn) were restored in toluene/THF 8 : 2 with 5.0 mol% CuOAc and 6.0 mol% L9 as the catalyst–ligand combination (entry 14).

We next investigated the scope of ketones using L1 in the anti-selective procedure and L9 in the syn-selective setup (Conditions A and B, Scheme 2). Acetophenones with various substituents in the para position, including electron-donating groups (as in 1b, c) and halogens (as in 1d–f), exhibited high reactivity and stereoselectivity. A carboxyl group was compatible (as in 1g), thus further emphasizing the functional-group tolerance of this reaction. 1h and i with meta substitution also gave satisfactory results. The reaction of ortho-methyl-substituted 1j was successful under Condition B and yielded syn-4ia with 98% ee (anti-4ja: 80% ee); conversely, poor stereoselectivity was obtained under Condition A. Pyridyl-substituted 1l reacted smoothly under Condition B and furnished syn-4la with good diastereoselectivity (d.r. = 90 : 10) and enantioselectivity (90% ee); in turn, the reaction of 1l under Condition A produced anti-4la with a moderate ee value. Aside from aromatic methyl ketones, propiophenone (1m), which had not been compatible with Morken’s44 and Hoveyda’s17b catalytic system (cf. Scheme 1), also furnished anti-4ma in excellent yield and good enantioselectivity with moderate diastereoselectivity under Condition A; B afforded the target compound in a similar yield yet with a high diastereomeric ratio and a markedly diminished ee value. Interestingly, 2b, unsaturated keto in 1n reacted regioselectively (1,2- over 1,4-addition) with good to excellent diastereoselectivity; syn-4na was the major product under both Condition A and B. Moreover, dialkyl ketone 1o converted into the corresponding products anti- and syn-4oa under A and B but with low diastereoselectivity likely due to the little steric differentiation between the methyl and methylene groups attached to the carbonyl carbon atom.

We then examined the scope of 1,3-dienes (Scheme 3). Isoprene (2a) could be replaced by buta-1,3-diene (2b),

| Entry | Ligand | Yield(%) | d.r. (anti : syn) | anti-4aa (%) | syn-4aa (%) |
|-------|--------|----------|------------------|--------------|-------------|
| 1     | L1     | 53       | 71 : 29          | 60           | 21          |
| 2     | L2     | 88       | 66 : 34          | 64           | 10          |
| 3     | L3     | 96       | 68 : 32          | 68           | 30          |
| 4     | L4     | 94       | 80 : 20          | 90           | 64          |
| 5     | L5     | 75       | 42 : 58          | 43           | 32          |
| 6     | L6     | 92       | 35 : 65          | 6            | 35          |
| 7     | L7     | 43       | 28 : 72          | 35           | 2           |
| 8     | L8     | 94       | 44 : 56          | 13           | 22          |
| 9     | L9     | 45       | 23 : 77          | 22           | 61          |
| 10    | L10    | 98       | 23 : 77          | 13           | 80          |
| 11    | L11    | 80       | 22 : 78          | 72           | 88          |
| 12    | L12    | 98       | 23 : 77          | 74           | 88          |
| 13    | L13    | 61       | 15 : 85          | 79           | 94          |
| 14    | L14    | 98       | 13 : 87          | 71           | 93          |
| 15    | L15    | 65       | 28 : 72          | 71           | 87          |
| 16    | L16    | 37       | 47 : 53          | 0            | 37          |
| 17    | L17    | 29       | 49 : 51          |  —           |  —          |

Table 1  Selected examples of the optimization of the borylative hydroxyalkylation of 1,3-dienes

a Unless otherwise noted, the reactions were performed with 1a (0.2 mmol), 2a (1 mmol), and B2(pin)2 (0.3 mmol) in THF (2 mL).

b Combined NMR yield determined by 1H NMR spectroscopy with CH3Br2 as an internal standard.

c Determined by HPLC analysis on chiral stationary phases. d CuOAc instead of CuCl. e Toluen instead of THF. f Run at –30 °C. g The other enantiomer was obtained. h Run at –20 °C. i 0.4 mmol scale, 5.0 mol% CuOAc and 6.0 mol% L9 were used and toluene/THF 8 : 2 instead of THF.
myrcene (2c), its functionalized derivative 2d, and 2,3-dimethylbuta-1,3-diene (2e). Yields were generally good but stereoselectivities ranged from poor to good under Condition A. In contrast, good to excellent stereoselectivities were observed for these 1,3-dienes under Condition B, e.g., d.r. = 96 : 4 and 92% ee for 1a → syn-4na and d.r. = 93 : 7 and 91% ee for 1a → syn-4ma. In the case of 2-aryl-substituted 1,3-diene 1f, diastereodivergency was not achieved. Subjecting 1f to Condition A afforded syn-4af in low yield as a single syn-isomer (not shown). However, applying Condition B at −5 °C significantly improved the yield and furnished the syn-4af with d.r. > 98 : 2 and 85% ee.

To explore synthetic transformations of these tertiary homoallylic alcohols (Scheme 4), a scale-up synthesis of syn-4aa (1.0 mmol) under Condition B was done without any loss in efficiency and selectivity (see the ESI†). The primary alkyl borane generated by the multicomponent reaction was subjected to a Suzuki–Miyaura coupling to afford syn-5 in 83% yield (Scheme 4, top). The versatility of the diol products 4 is illustrated for several transformations (Scheme 4, bottom). The 1,1-disubstituted double bond in antı-4ja was hydroge-
nated over Pd/C to produce anti-6 in 87% yield. The hydroxy group in syn-4aa was replaced by an azide group through an SN2 reaction of an intermediate mesylate with NaN3 (syn-4aa → syn-7). Pyran syn-8 was synthesized from syn-4ab by sequential alcohol allylation and ring-closing metathesis. Of note, a chemoselective tosylation of the primary alcohol in syn-4aa followed by a 4-exo-tet ring closure allowed for the construction of enantioenriched, trisubstituted oxetane trans-9 in 86% yield.

**Conclusion**

In summary, we have developed an efficient copper-catalyzed diastereodivergent and enantioselective borylative coupling of 1,3-dienes and ketones. Using a Feringa-type ligand L1, the
reaction yielded anti-configured tertiary homoallylic alcohols while a switch to josiphos ligand L9 resulted in syn selectivity (see the ESI for a discussion of the reaction mechanism). This three-component coupling reaction represents a useful method for the preparation of stereochemically diverse tertiary alcohols bearing versatile alkenyl and boryl motifs from feedstock 1,3-dienes, ketones, and B$_3$(pin)$_3$. The synthetic utility of the reaction was showcased by several transformations.

**Conflicts of interest**

There are no conflicts to declare.

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