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O-Monoacyltartaric Acid Catalyzed Enantioselective Conjugate Addition of a Boronic Acid to Dienones: Application to the Synthesis of Optically Active Cyclopentenones

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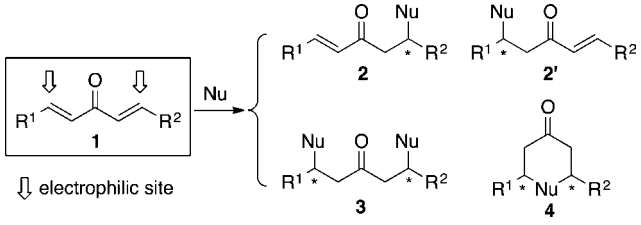
Supporting Information

ABSTRACT: Enantioselective conjugate addition of styrylboronic acid to dienones was effectively catalyzed by an *O*-monoacyltartaric acid to afford monostyrylated products with good enantioselectivity. The RCM of the monostyrylated products using the Hoveyda–Grubbs II catalyst afforded optically active cyclopentenones, including a synthetic intermediate of the antitumor agent TEI-9826. The study shows that a diene additive such as 1,6-heptadiene or diallyl ether was essential for the RCM.

Dienones **1** (Scheme 1) are readily available via aldol condensations between acetone and an aldehyde ($R^1 = R^2$)[1] or between an enone and an aldehyde ($R^1 \neq R^2$).[2] The corresponding Horner–Wadsworth–Emmons reactions are also applicable to the preparation of **1**.[3,4] As dienones **1** possess two electrophilic sites, the enantioselective conjugate addition[5] of nucleophiles to **1** is an interesting challenge in regio- and chemoselectivities (Scheme 1). Several optically active products **2**–**4** with stereogenic center(s) at the carbonyl β-position(s) can be generated. Selective formation of a monoadduct **2** or **2′** may allow further functionalization because of the remaining unsaturated bond.

Scheme 1. Conjugate Addition to Dienones 1

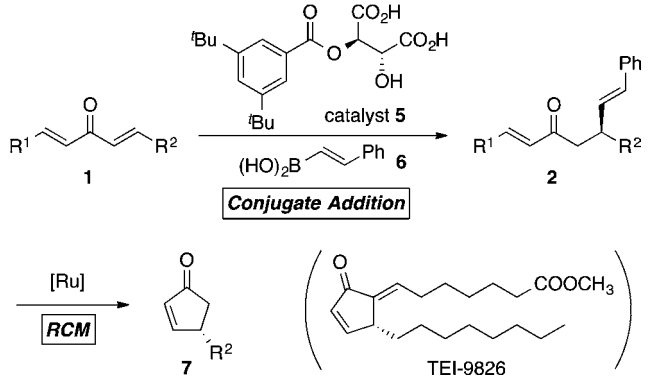


Several research groups have focused on this issue and developed highly enantioselective methods: Cu-catalyzed addition of dialkylzinc,[6] Pd- or Ni-catalyzed addition of allylboronate,[7] Rh-catalyzed conjugate alkynylation,[8] and organocatalyzed cyclization with malononitrile.[9] However, such examples are limited, despite the availability of dienones **1**.[10]

Meanwhile, non-metal-promoted conjugate addition of alkenylboronate to enones was first discovered by Suzuki and co-workers.[11] More than 15 years later, Chong and co-workers described the first organocatalyzed enantioselective method utilizing 3,3′-disubstituted BINOL derivatives as catalysts.[12] Chiral secondary amines,[13] thiourea derivatives,[14] other BINOL derivatives,[15] or a resin-supported peptide[16] catalyzed the enantioselective addition of boronic acids or their esters to enones or enals, respectively.[17] However, the application of these enantioselective methods to the reaction of multiconjugated carbonyl compounds **1** has not been explored.[18]

We recently reported that *O*-(3,5-di-*tert*-butylbenzoyl)tartaric acid **5** (Scheme 2) effectively catalyzed the enantioselective conjugate addition of boronic acids to enones.[19] We therefore envisaged that the reaction of dienones **1** and styrylboronic acid (**6**) might be catalyzed by **5** to selectively furnish monostyrylated product **2** and that the Ru-catalyzed RCM[20] of diene products **2** might result in optically active cyclopentenones **7**, which are an important structural motif in natural products and pharmaceuticals, such as the antitumor agent TEI-9826[21] (Scheme 2). Helmchen and co-workers described the asymmetric synthesis of **7** via Ir-catalyzed enantioselective allylic alkylation, vinylation of

Scheme 2. Asymmetric Synthesis of Cyclopentenones via Enantioselective Conjugate Addition and RCM



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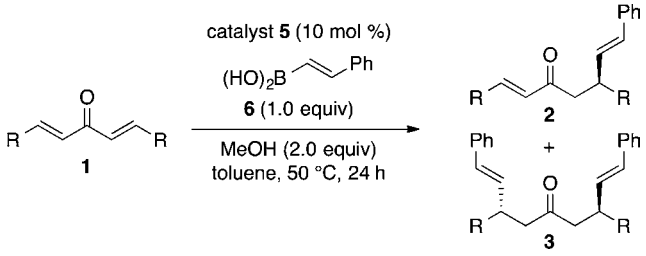
the Weinreb amide products, and the RCM of the resulting terminal dienes.[21b,c] Our strategy may be challenging not only because of the aforementioned selectivity issues in the conjugate addition to dienones **1** but also because of the low reactivity expected for conjugated internal dienes **2** in the RCM.

We initially investigated the reaction of dibenzylidene acetone (**1a**) and styrylboronic acid (**6**) with tartaric acid derived catalyst **5** under the conditions reported previously (1.2 equiv of **6** and 2.4 equiv of methanol in toluene at 50 °C; Table 1, entry 1). The

Table 1. Conjugate Addition of Styrylboronic Acid (6) to Symmetrical Dienones 1[a]



entry	R (1)	2	yield (%)	ee (%)	3	yield (%)
1[b]	Ph (**1a**)	**2a**	79	86	**3a**	16[c]
2[d]	Ph (**1a**)	**2a**	78	86	**3a**	16
3	Ph (**1a**)	**2a**	81	86	**3a**	9
4[e]	Ph (**1a**)	**2a**	42	86	**3a**	58[f]
5	*p*-BrC_6H_4 (**1b**)	**2b**	52	86	**3b**	21
6	*p*-$MeOC_6H_4$ (**1c**)	**2c**	68	90	**3c**	12
7	2-thienyl (**1d**)	**2d**	76	88	**3d**	8
8	1-naphthyl (**1e**)	**2e**	68	94	**3e**	15
9	*n*-C_8H_{17} (**1f**)	**2f**	56	89	**3f**	15

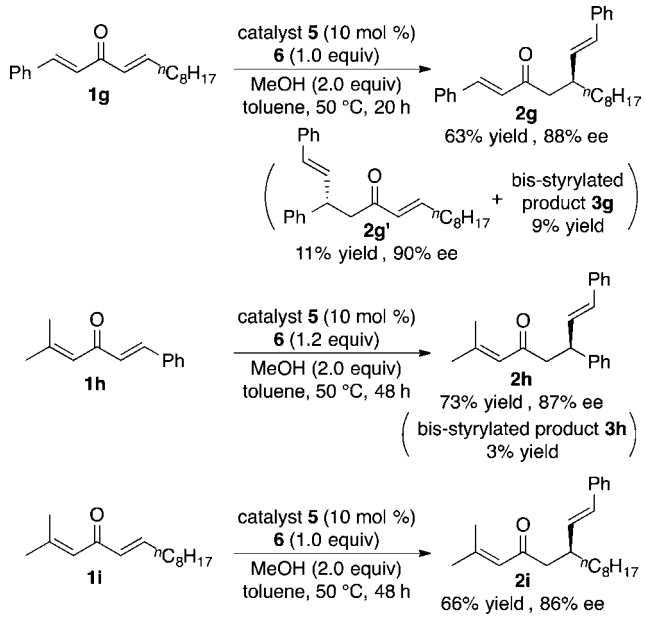
[a]Unless otherwise noted, the reaction was conducted using dienone **1** (0.3 mmol), styrylboronic acid (**6**) (0.3 mmol), methanol (0.6 mmol), and catalyst **5** (10 mol %) in toluene (1 mL) at 50 °C. [b]With **1** (0.3 mmol), **6** (0.36 mmol), methanol (0.72 mmol), and **5** (0.03 mmol). [c]*dl*/*meso* = 84/16, 99% ee (*dl*-isomer). [d]For 14 h. [e]With **1** (0.15 mmol), **6** (0.36 mmol), methanol (0.72 mmol), and **5** (0.03 mmol) for 48 h. [f]*dl*/*meso* = 87/13, 99% ee (*dl*-isomer).

desired monostyrylated product (*S*)-**2a** was obtained in good yield with good enantioselectivity and good chemoselectivity (selectivity between monoadduct **2** and bis-adduct **3**). The bis-styrylated product **3a** was obtained as a mixture of the *dl*- and *meso*-isomers (84:16), and the enantiomeric excess of the *dl*-isomer was 99% ee. These results indicate that the second conjugate addition is independent of the first addition with nearly the same enantioselectivity. To suppress the formation of **3a**, the reaction time was reduced to 14 h, but the chemoselectivity was not improved (entry 2). Simply decreasing the amount of boronic acid **6** to 1 equiv suppressed the formation of undesired **3a** (entry 3). The reaction using an excess amount (2.4 equiv) of the boronic acid mainly afforded bis-adduct **3a** after 48 h with almost the same stereoselectivity as entry 1 (entry 4).

Under the conditions optimized for dienone **1a** (entry 3), the reactions of other symmetrical dienones **1b**–**f** were performed (entries 5–9). Dienone **1b** with electron-deficient *p*-bromophenyl groups showed lower chemoselectivity than **1a** (entry 5), though the enantioselectivity of product **2b** was the same as that of **2a**. Conversely, dienones **1c**–**e** (entries 6–8) bearing electron-rich aromatic rings tended to have higher enantioselectivities than unsubstituted **1a**. The highest enantioselectivity (94% ee) was observed for the reaction of **1e** bearing bulky and electron-rich 1-naphthyl groups (entry 8). We speculate that electron-rich substituents tighten the transition state for the enantio-determining C–C bond formation, leading to high enantioselectivity;[22] the carbonyl oxygen atoms of these enones have higher Lewis basicity and, thus, coordinate more strongly to the boron atom of the styrylboronic acid/catalyst complex.[23] The reaction of alkyl group substituted dienone **1f** afforded the desired monostyrylated product **2f** with a somewhat higher enantioselectivity, although a significant amount of bis-styrylated product **3f** was obtained (entry 9).

We next studied the reaction of unsymmetrical dienones **1g**–**i** (Scheme 3). The styryl group was chemoselectively added to the

Scheme 3. Reaction of Unsymmetrical Dienones



alkyl-substituted β-position of **1g** with good enantioselectivity.[24] The reactions of **1h** and **1i** occurred at the less substituted β-position to afford adducts **2h** and **2i**, respectively, with high chemoselectivities and good enantioselectivities.

Using the obtained monostyrylated products, the synthesis of cyclopentenones via the RCM[25] was investigated (Table 2). We first examined the Schrodi–Grubbs catalyst[26] in the presence of 1,6-heptadiene because Fukuyama and co-workers have recently reported in a total synthesis that this combination was effective for the RCM of a diene with low reactivity.[27] Under their conditions (addition of 5 mol % of catalyst every 24 h; total 15 mol %), the RCM of **2a** afforded the desired cyclopentenone **7a** in a moderate yield (entry 1). The Grubbs II catalyst[20] also showed a similar activity with the diene additive (entry 2), whereas the Grubbs I catalyst[20] did not catalyze the cyclization (entry 3). The use of the Hoveyda–Grubbs II catalyst[28] further improved the yield (entry 4). We found that portionwise addition of the catalyst was not necessary, as the same yield was obtained when the catalyst (15 mol %) was added in one portion (entry 5). Decreasing the amount of the catalyst to 10 mol % lowered the yield (entry 6); however, changing the solvent from benzene to toluene and elevating the temperature to 80 °C dramatically improved the yield, even with 10 mol % catalyst (entry 7). The addition of twice the amount of 1,6-heptadiene did not improve the yield (entry 8), but notably diene **2a** did not cyclize in the absence of the diene additive (entry 9). Diallyl ether

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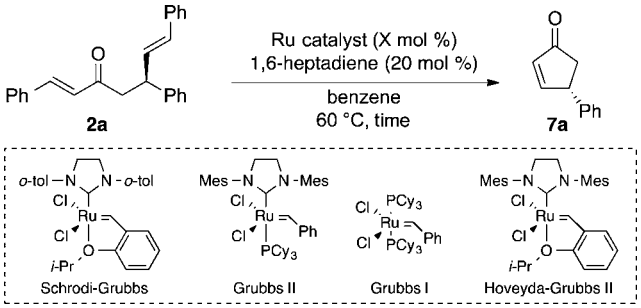
Table 2. RCM of Monostyrylated Products



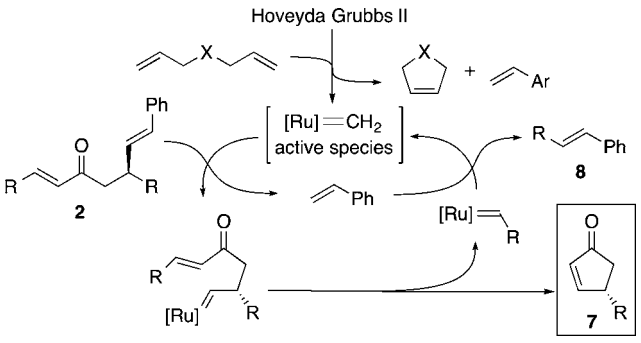
entry	Ru catalyst	X	time (h)	yield (%)
1[a]	Schrodi–Grubbs	15	72	56
2[a]	Grubbs II	15	72	56
3[a]	Grubbs I	15	72	0
4[a]	Hoveyda–Grubbs II	15	72	84
5[b]	Hoveyda–Grubbs II	15	24	84
6[b]	Hoveyda–Grubbs II	10	24	73
7[b,c]	Hoveyda–Grubbs II	10	24	98
8[b,c,d]	Hoveyda–Grubbs II	10	24	85
9[b,c,e]	Hoveyda–Grubbs II	10	24	0
10[b,c,f]	Hoveyda–Grubbs II	10	24	81

[a]The catalyst (5 mol %) was added every 24 h (total 15 mol %). [b]The catalyst was added in one portion. [c]In toluene at 80 °C. [d]With 1,6-heptadiene (0.4 equiv). [e]Without 1,6-heptadiene. [f]With diallyl ether (0.2 equiv) instead of 1,6-heptadiene.

was found to be as effective an additive as 1,6-heptadiene (entry 10).

The effect of the diene additives on this reaction system was significant and may be attributed to the generation of an active ruthenium methylidene complex in situ.[29] This complex would promote the RCM of less reactive conjugated internal alkenes such as **2** (Scheme 4). Catalytic amounts of the diene additive can be used because the methylidene species is regenerated along with the formation of stable β-substituted styrenes **8**.

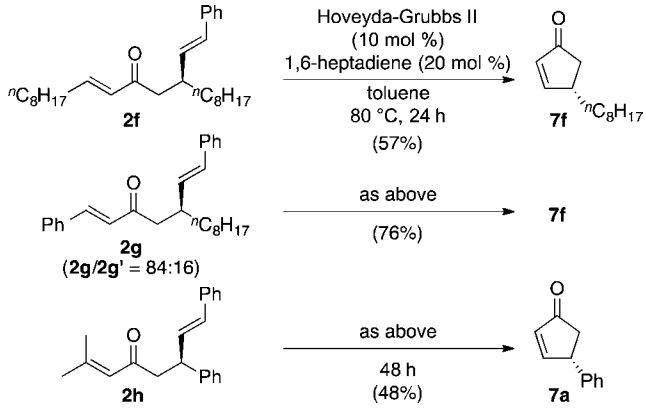
Scheme 4. Probable Catalytic Cycle



After establishing the effective conditions for the RCM, the reactions of diene products **2f–h** were examined (Scheme 5). The reaction of **2f** or **2g** afforded cyclopentenone **7f**, which is a synthetic intermediate of TEI-9826.[21b,c] Though our synthetic process is not atom-economical,[30] it is step-economical[31] because dienone substrates are readily available. The even less reactive trisubstituted enone **2h** could be cyclized using the same catalyst system to afford cyclopentenone **7a** in a moderate yield.

In summary, we have demonstrated that an *O*-monoacyltartaric acid effectively catalyzed the conjugated addition of

Scheme 5. RCM of Products 2f–h



styrylboronic acid to symmetrical and unsymmetrical dienones to afford monostyrylated adducts with good enantioselectivity. The RCM of the diene products using the Hoveyda–Grubbs II catalyst proceeded smoothly in the presence of a diene additive to afford optically active cyclopentenones, including a synthetic intermediate of the antitumor agent TEI-9826. Further improvements of the chemo- and enantioselectivities and the application of tartaric acid derived catalysts to other reaction systems are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of all new products. 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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