Catalytic Asymmetric Aldehyde Prenylation and Application in the Total Synthesis of ()-Rosiridol and ()-Bifurcadiol

COMMUNICATION

Catalytic Asymmetric Aldehyde Prenylation and Application in the Total Synthesis of (–)-Rosiridol and (–)-Bifurcadiol

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Chiral phosphoric acid-catalyzed asymmetric aldehyde prenylation has been established using an α,α-dimethyl allyl boronic ester. The transformation provides an expedient access to a wide array of aryl, heteroaryl, aryl-substituted alkenyl as well as primary and secondary aliphatic homoprenyl alcohols with excellent asymmetric induction. The utility of this asymmetric catalysis strategy has been demonstrated through a short and efficient total synthesis of the two natural products (–)-rosiridol and (–)-bifurcadiol.

Enantiomerically enriched homoprenyl alcohols are not only versatile building blocks,[1] but also widely present as key motifs in pharmaceutically active compounds and natural products (Figure 1).[2]

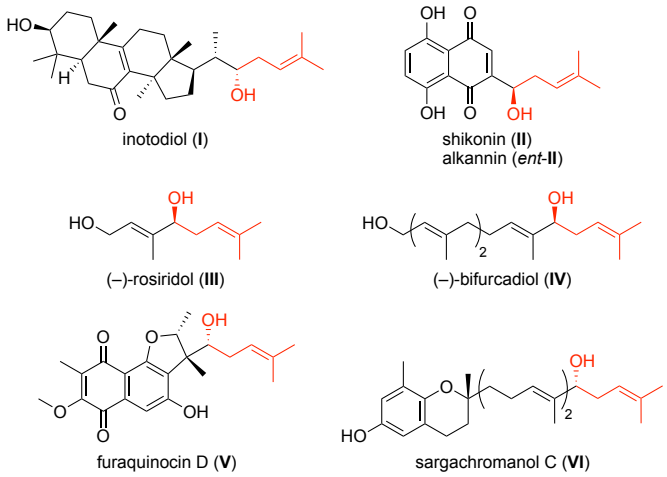

Figure 1. Selected natural products containing an enantioenriched homoprenyl alcohol motif.

Indeed, inotodiol (**I**) displays significant anti-tumor activity, including human cervical cancer.[3] Shikonin (**II**) exhibits anti-bacterial and anti-tumor activities while its enantiomer (alkannin) has been used as anti-oxidant, anti-tumor, and anti-thrombotic agents, and in wound healing.[4] (–)-Rosiridol (**III**) and its glycosylated derivatives inhibit monoamine oxidase B (MAO B), which is involved in neurodegenerative diseases.[5] (–)-Bifurcadiol (**IV**) displays anti-ulcer and anti-tumor activities.[6] Furaquinocin D (**V**) shows a wide range of biological effects including anti-hypertensive activity, inhibition of platelet aggregation and coagulation.[7] Sargachromanol C (**VI**) has been identified as a potential anti-cancer and anti-mutagenic agent as well as an inhibitor of Na^+/K^+ ATPase and isocitrate lyase.[8]

In this context, the invention of efficient *asymmetric catalysis* methods to assemble enantiomerically enriched homoprenyl alcohols[9] and the corresponding natural products or potential drugs represents a significant task for synthetic organic chemists.[10] To date, two types of synthetic strategies have been documented to achieve this goal; reduction (C–H bond formation) and C–C bond formation (Scheme 1). The first approach relies on the asymmetric reduction of prenyl ketones using a *stoichiometric* amount of a chirally modified B-based[11a–c] or Al-based[11d] reductant; accordingly, the asymmetric total syntheses of shikonin (**II**),[11a,b] alkannin (*ent*-**II**),[11a,b] (–)-rosiridol (**III**),[11c] and (–)-bifurcadiol (**IV**)[11d] have been described (Scheme 1–1). The second approach relies on the use of a chiral reagent or catalyst in order to access enantioenriched homoprenyl alcohols *via* C–C bond formation. Suzuki *et al.* reported the total synthesis of (–)-furaquinocin D (**V**) from an enantioenriched terminal epoxide and an alkenyl stannane in the presence of stoichiometric amounts of BuLi and BF_3•OEt_2 (single example; Scheme 1–2).[12] Here, the reaction proceeds *via* Sn–Li transmetalation followed by boron-mediated epoxide ring-opening with the *in situ*-generated alkenyl lithium species. Loh *et al.* reported a TfOH-catalysed prenylation using aldehydes and an enantioenriched prenyl 1,5-diol (8 examples; Scheme 1–3a);[13] after initial condensation, the chirality transfer proceeds *via* an oxonia-Cope rearrangement followed by hydrolysis to give the corresponding homoprenyl alcohols (87–98% *ee*). Cozzi and Umani-Ronchi *et al.* reported a catalytic asymmetric Nozaki–Hiyama reaction using benzaldehyde and prenyl chloride in the presence of an enantioenriched chromium complex and stoichiometric amounts of Mn(0) and Me_3SiCl to afford the corresponding homoprenyl alcohol with 42% *ee* (single example; Scheme 1–3b);[14] While catalytic asymmetric prenylation across C=C double bonds with high asymmetric induction has been established,[15] the use of

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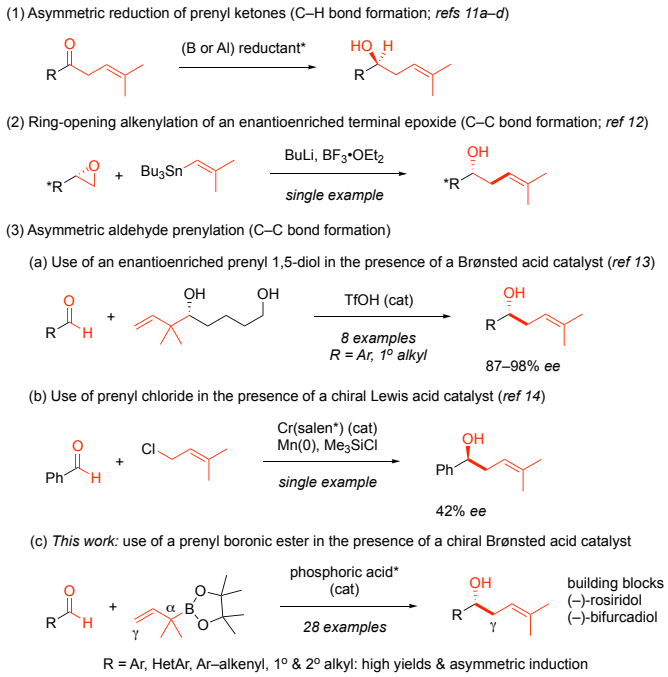
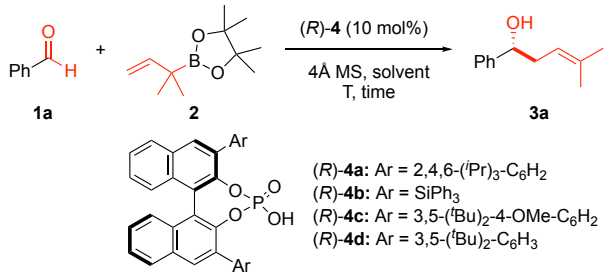
carbonyl electrophiles to access enantioenriched homoprenyl alcohols has remained elusive.[16] Since the asymmetric γ-regioselective allyl boration of aldehydes catalysed by an enantioenriched Brønsted acid provides a short and efficient access to homoallyl alcohols,[17] we have anticipated the possibility of using an α,α-dimethyl allyl boronic ester[18] to create an unprecedented *catalytic* entry to homoprenyl alcohols with high asymmetric induction (Scheme 1–3c). Accordingly, complex chiral molecules containing a homoprenyl alcohol motif could be concisely installed by asymmetric catalysis. In this communication, we describe a simple, general, and highly regio- and enantioselective aldehyde prenylation controlled by an (*R*)-BINOL-derived phosphoric acid catalyst, and applications to the total synthesis of (–)-rosiridol (**III**) and (–)-bifurcadiol (**IV**).



Scheme 1. Access to enantioenriched homoprenyl alcohols: literature background and this work's approach.

In our initial prenylation model study, benzaldehyde (**1a**) was used with α,α-dimethyl allyl boronic ester **2** in toluene in the presence of 4Å molecular sieves (Table 1). In the absence of a catalyst, homoprenyl alcohol **3a** (racemic) was formed at room temperature in 82% yield (5 h; entry 1). In order to suppress this background reaction in view of an intended asymmetric version, a chiral Brønsted acid catalysis strategy was applied at 0 °C. In the presence of 10 mol% of (*R*)-BINOL-derived chiral phosphoric acid (*R*)-**4a**, product **3a** was obtained in 86% yield with 73% *ee* (entry 2). The catalytic use of other chiral phosphoric acids (*R*)-**4b–d** has proved less effective (26–64% *ee*; entries 3–5). Similarly, the reactions using (*R*)-**4a** in THF and DCM gave product **3a** in only 60% *ee* and 48% *ee*, respectively (entries 6 and 7). Next, we investigated the effect of the reaction temperature on the asymmetric induction (entries 8–12). Gratifyingly, **3a** was formed with 95% *ee* at –20 °C (entry 8); the best result was obtained at –60 °C over 32 h (93% yield, 98% *ee*; entry 12). A control experiment in the absence of 4Å molecular sieves resulted in the formation of **3a** with only 76% *ee* (entry 13); this result suggests that traces of water display a detrimental effect on the asymmetric induction, likely by disturbing the H-bond donor ability of the chiral catalyst. Finally, the effect of the catalyst loading was probed thereby confirming that 10 mol% was the appropriate amount for this transformation (entries 14 and 15). The standard reaction conditions for the following studies refer to the optimised conditions displayed in entry 12 of Table 1: **2** (1.5 equiv), (*R*)-**4a** (10 mol%), 4Å MS, toluene, –60 °C.

Table 1. Optimization of reaction conditions.[a]

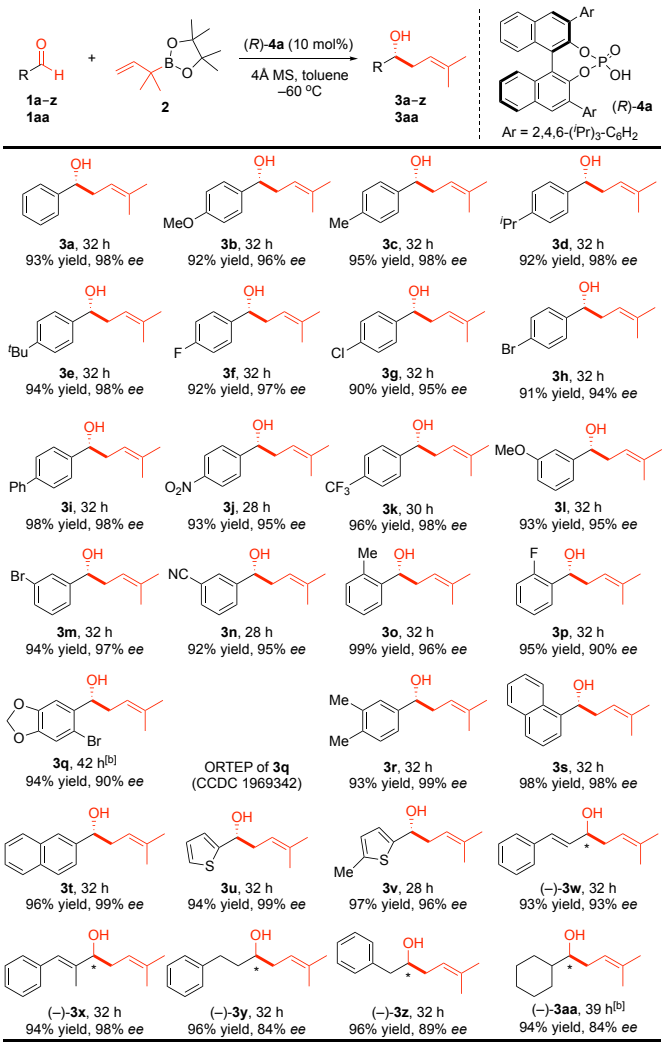


entry	catalyst	solvent	T / °C	time / h	yield / %[b]	*ee*[c]
1	–	toluene	rt	5	82	0
2	**4a**	toluene	0	12	86	73
3	**4b**	toluene	0	18	92	26
4	**4c**	toluene	0	10	85	56
5	**4d**	toluene	0	13	92	64
6	**4a**	THF	0	12	89	60
7	**4a**	DCM	0	10	93	48
8	**4a**	toluene	–20	20	90	95
9	**4a**	toluene	–30	24	94	95
10	**4a**	toluene	–40	28	92	96
11	**4a**	toluene	–50	30	89	97
12	**4a**	toluene	–60	32	93	98
13[d]	**4a**	toluene	–60	36	89	76
14[e]	**4a**	toluene	–60	38	90	83
15[f]	**4a**	toluene	–60	26	92	98

[a] Reaction conditions (unless otherwise specified): **1a** (0.10 mmol), **2** (0.15 mmol), (*R*)-**4** (10 mol%), 4 Å MS (25 mg), solvent (0.3 mL). [b] Isolated yield. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [d] In the absence of 4Å MS. [e] 5 mol% of (*R*)-**4a**. [f] 15 mol% of of (*R*)-**4a**.

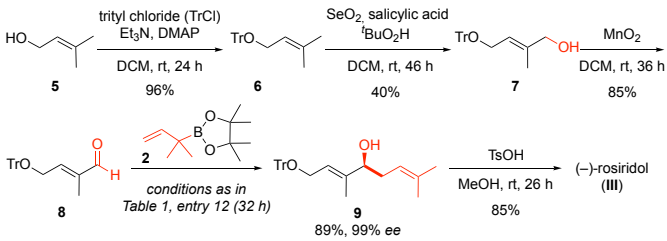
The optimal reaction conditions were applied to a wide variety of aldehydes to probe the versatility of our methods (Scheme 2). Initially, the effect of diverse substituents at the *para*, *meta*, and *ortho* positions of the aromatic ring was examined. The use of aromatic aldehydes bearing *para*-located electron-donating, neutral, and electron-withdrawing groups gave the corresponding homoprenyl alcohols **3b–k** with 94–98% *ee*. *Meta*-located substituents (MeO, Br, CN) were also tolerated; the corresponding products **3l–n** were formed with 95–97% *ee*. The use of aromatic aldehydes with an *ortho*-located F atom and Me group gave homoprenyl alcohols **3o** and **3p** with 90% *ee* and 96% *ee*, respectively. The use of 6-bromopiperonal (**1q**) under slightly modified conditions provided product **3q** with 90% *ee*; the absolute configuration of (+)-**3q** was determined to be *R* based on an X-ray crystallographic analysis.[19] By analogy, the absolute configuration of all other aromatic homoprenyl alcohols was also assigned to be *R*. Product **3r**, derived from 3,4-dimethylbenzaldehyde, was produced with 99% *ee*. Naphthalene- and thiophene-derived aldehydes were converted into the corresponding homoprenyl alcohols **3s–v** with 96–99% *ee*. In addition, aryl-substituted alkenyl aldehydes **1w** and **1x** were used to give the corresponding products **3w** and **3x** with 93% *ee* and 98% *ee*, respectively. Finally, challenging primary and secondary aliphatic aldehydes **1y–z** and **1aa** were used to provide homoprenyl alcohols **3y–z** and **3aa** with 84–89% *ee*.

Scheme 2. Scope of aldehydes.[a]

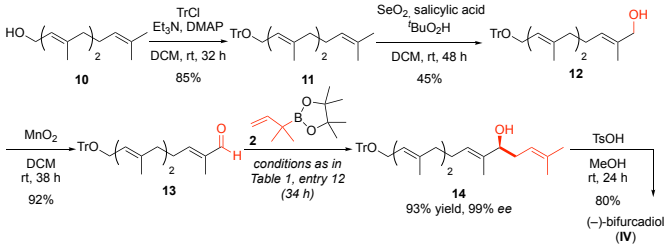


[a] Reaction conditions (unless otherwise specified): **1** (0.10 mmol), **2** (0.15 mmol), (*R*)-**4a** (10 mol%), 4Å MS (25 mg), solvent (0.3 mL); yield of isolated product; *ee* values were determined by chiral HPLC analysis. [b] The reaction was performed in DCM at –78 °C.

Next, we focused on applying this asymmetric *catalysis* method to the total synthesis of the natural products (–)-rosiridol (**III**) and (–)-bifurcadiol (**IV**). As mentioned before, the total synthesis of these compounds was achieved through a critical asymmetric reduction of the corresponding prenyl ketone using a *stoichiometric* amount of a chiral reductant.[11c,d] Moreover, the construction of the prenyl ketone substrates required three steps: prenylation of aldehyde **8** (*cf.* Scheme 3) or **13** (*cf.* Scheme 4); oxidation of the resulting alcohol to the corresponding ketone; asymmetric reduction. Such approach is arguably more tedious and less sustainable than a direct *catalytic* asymmetric prenylation of **8** or **13**. With this in mind, we synthesised alkenyl aldehyde **8** (Scheme 3). Distinct from the reported synthesis,[11c] we installed a trityl (Tr) protecting group on primary alcohol **5** in 96% yield. The resulting ether **6** underwent standard allylic oxidation to form alcohol **7** in 40% yield. Subsequent oxidation of allylic alcohol **7** using MnO_2 gave substrate **8** in 85% yield. The catalytic asymmetric prenylation of **8** using **2** was carried out under the optimised conditions to form homoprenyl alcohol **9** in 89% yield with 99% *ee* (Scheme 3). Finally, the removal of the protecting group gave (–)-rosiridol (**III**) in 85% yield. Based on the reported *S*-configuration of **III**,[11c] the stereogenic centre in alcohol **9** must be consequently also *S*-configured. Therefore, the C–C bond formation between alkenyl aldehyde **8** and **2** (prenylation) must have occurred from the aldehyde's *Re*-face; interestingly, this would be opposite to the case of aromatic aldehydes (*Si*-face attack; *cf.* Scheme 2). Compared with the reported *stoichiometric* methods,[11] the present synthesis is shorter and the stereogenic centre was formed by asymmetric *catalysis*. Encouraged by this success, a short total synthesis of (–)-bifurcadiol (**IV**) was also achieved in five similar steps starting from alcohol **10** (Scheme 4).[11d] Here, the precursor to **IV**, homoprenyl alcohol **14**, was formed under the optimised conditions in 93% yield with 99% *ee* (Scheme 4); the absolute configuration of the created stereogenic centre in **14** was determined as *S* by comparison with the earlier report on **IV**.[11d] Thus, it turns out that the enantiofacial discrimination using alkenyl aldehydes is opposite to the one using aromatic aldehydes.



Scheme 3. Synthetic route to (–)-rosiridol (**III**).



Scheme 4. Synthetic route to (–)-bifurcadiol (**IV**).

Conclusions

In summary, we have established the first example of highly enantioselective general aldehyde prenylation[16] controlled by a chiral phosphoric acid catalyst. A broad range of enantioenriched aryl, heteroaryl, aryl-substituted alkenyl, as well as primary and secondary aliphatic homoprenyl alcohols have been constructed regioselectively in high yields with excellent asymmetric induction. The synthetic pathways to the two natural products (–)-rosiridol and (–)-bifurcadiol were streamlined by virtue of this catalytic asymmetric prenylation method. Further applications of the α,α-dimethyl allyl boronic ester in other asymmetric reactions will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Province (2018CFA084), and Wuhan Morning Light Plan of Youth Science and Technology (2017050304010314).

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19 CCDC 1969342 contains the supplementary crystallographic data (**3q**) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.