Stereoselective Catalysis

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Catalytic Enantioselective Alkylation of Substituted Dioxanone Enol Ethers: Ready Access to C(α)-Tetrasubstituted Hydroxyketones, Acids, and Esters**

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The catalytic enantioselective formation of tetrasubstituted α-alkoxycarbonyl compounds is an ongoing challenge to synthetic chemists.[1] Fully substituted α-hydroxyesters and acids comprise essential components of, and building blocks for, many bioactive natural products (see Figure 1). These include quinic acid (**1**), cytotoxic leiodolide A (**2**),[2] and the anticancer agents in the harringtonine series (**3a–f**), whose activities depend dramatically on the presence and composition of an α-hydroxyester side-chain.[3] While many approaches to these important moieties exist,[4,5] we envisioned applying our recently developed palladium-catalyzed methods for the formation of enantioenriched all-carbon quaternary stereocenters in cyclic alkanones[6] to a general synthesis of C(α)-tetrasubstituted hydroxy carbonyl compounds.[7]

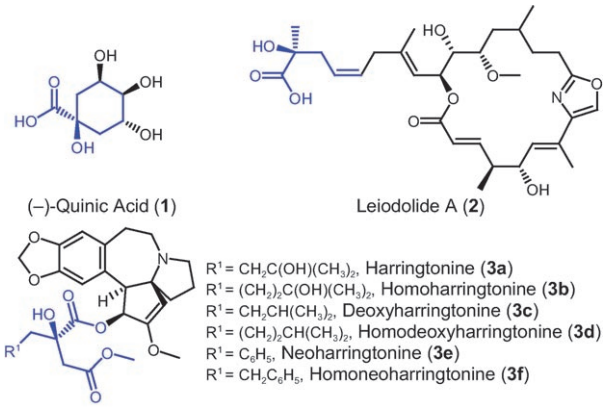
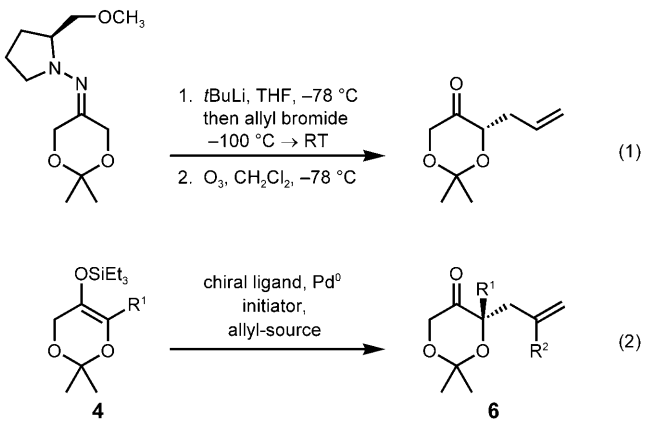


Figure 1. Natural products containing α-hydroxyesters and acids.

For this application, we chose to incorporate the α-oxygenation into a cyclic motif, the 2,2-dimethyl-1,3-dioxan-5-one framework,[8] and employ this platform for the enantioselective synthesis of α-dialkyl ketones (Scheme 1, **6**, for example). Dioxanones are challenging alkylation substrates because standard conditions do not permit alkylation, but instead facilitate ketone reduction (e.g. lithium diisopropylamide, LDA, −78 °C), or self-condensation (e.g., lithium hexamethyldisilazide, LHMDS), accompanied by decomposition.[9] A technology that avoids this undesirable reactivity would represent a marked advance in dioxanone chemistry. For this purpose, Enders and co-workers have developed a diastereoselective α-alkylation that relies on chirality imparted by (+)-*S*-1-amino-2-methoxymethylpyrrolidine hydrazones, which can be cleaved in a subsequent step [Scheme 1, Eq. (1)]. We believed our catalytic palladium technology would be an ideal platform to provide access to valuable tetrasubstituted α-hydroxyketones, esters, and acids [Scheme 1, Eq. (2)].



Scheme 1. Alkylation strategies using the dioxanone framework.

We examined the conversion of silyl enol ether **4a**[10] into enantioenriched tetrasubstituted ketone **6a** under a variety of palladium-catalyzed conditions, beginning with the standard conditions developed for the all-carbon system (Table 1).[6] Triethylsilyl derivative **4a** was chosen for its stability and ease of synthesis, compared to the related trimethylsilyl compound. Treatment of silyl ether **4a** with $Pd(dmdba)_2$ (5 mol%, dmdba = bis(3,5-dimethoxybenzylidene)acetone),

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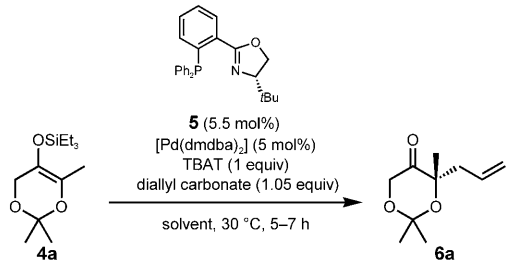
Table 1: Optimization of the enantioselective allylation of silyl enol ether **4a**.[a]



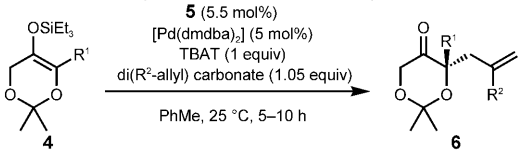
Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	THF	40	81
2[d]	Et_2O	59	89
3	1,4-dioxane	65	67
4	benzene	67	84
5	toluene	74	88

[a] Reactions were performed using 0.1 mmol of substrate in solvent (0.033 M) at 25 °C over 5–7 h unless stated otherwise. [b] Yields of isolated product. [c] Measured by chiral HPLC following conversion to **6b**.[12] [d] Performed at 30 °C and 0.0167 M.

(*S*)-*t*BuPHOX (**5**, 5.5 mol%),[11] $Bu_4NPh_3SiF_2$ (TBAT, 1 equiv), and diallyl carbonate (1.05 equiv) in THF at 25 °C (Table 1, entry 1) produced enantioenriched **6a** in 40% yield and 81% *ee*. Interestingly, the choice of solvent played a significant role in the selectivity of tertiary ether formation. In the optimal case, use of toluene as solvent furnished dioxanone **6a** in 74% yield and 88% *ee* (Table 1, entry 5).

We applied the optimized conditions to silyl enol ethers with diverse α-substituents, in combination with substituted allyl carbonates (Table 2). The asymmetric alkylation tolerates a variety of substituents at the α-position, including alkyl (Table 2, entries 1 and 2), benzyl (Table 2, entry 3), and alkenyl (Table 2, entries 7–9) moieties. Additionally, the reaction proceeds when the allyl group is substituted internally by methyl, chloro, or phenyl (Table 2, entries 4–7) to afford products in high yields and high entantiomeric excess.

Table 2: Substrate scope for enantioselective allylation.[a]

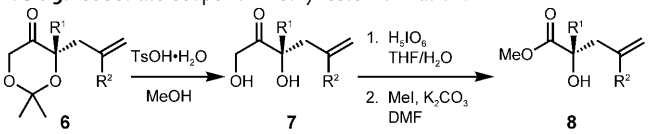


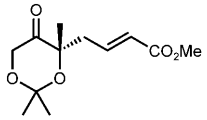
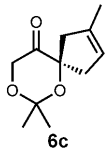
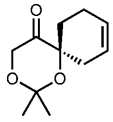
Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Me	H	86	87
2	Et	H	79	93
3	$PhCH_2$	H	85	86
4[d,e]	Me	Me	59	89
5[f]	Me	Cl[g]	59	92
6[h]	Me	Ph	73	94
7[e]	allyl	Me	93	88
8	2-methallyl	H	88	85
9	1-butenyl	H	83	92

[a] Reactions were performed with silyl enol ether (0.5 mmol) and diallyl carbonate (1.05 equiv) in PhMe (0.033 M) unless stated otherwise. When $R^1 = R^2 = H$, the reaction proceeds in 13% yield and 82% *ee*. [b] Yields of isolated product. [c] Measured by chiral GC or HPLC.[12] [d] Performed with trimethylsilyl precursor, 35 mol% TBAT in Et_2O (0.0167 M) at 25 °C. [e] Performed with dimethallyl carbonate (1.05 equiv). [f] Performed with dichloroallyl carbonate (1.05 equiv) at 35 °C. [g] Absolute stereochemistry has been assigned by analogy, except in this case, which was assigned by conversion into (+)-(*S*)-citramalic acid dimethyl ester.[12] [h] Performed with diphenylallyl carbonate (1.05 equiv).

Having established a general route to the enantioenriched tetrasubstituted dioxanone **6**, we developed a straightforward sequence to transform the α-alkoxyketone into the corresponding α-hydroxyester **8** (Table 3). To effect acetonide cleavage, enantioenriched product **6** is treated with catalytic *p*-toluenesulfonic acid ($TsOH \cdot H_2O$) in methanol or ethanol. Dihydroxyketone **7** is oxidatively cleaved in the presence of periodic acid, selectively removing the primary alcohol,[13] to generate the α-hydroxyacid. Subsequent methylation furnishes the tetrasubstituted enantioenriched α-hydroxyester **8**. These operations are tolerant of a number of substitutents, including alkyl (Table 3, entries 1–4), chloro (Table 3, entry 5), and aryl (Table 3, entries 3 and 6) groups. Further-

Table 3: Substrate scope for methyl ester formation.[a]

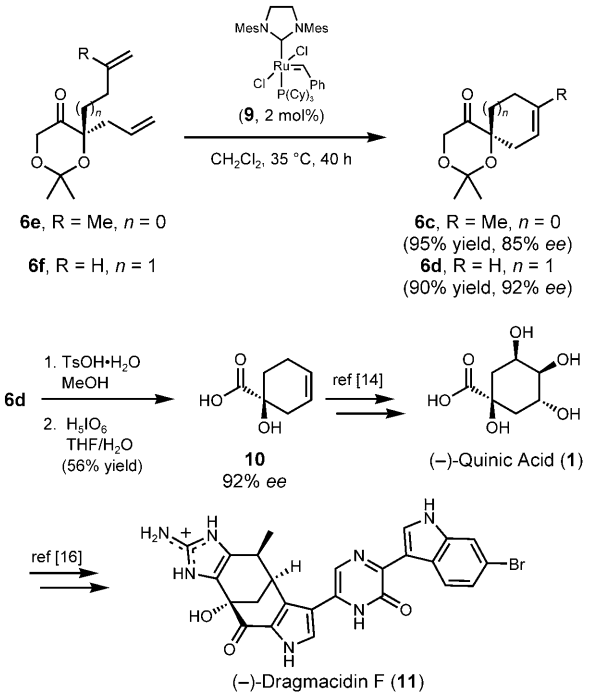


Entry	Substrate R^1	Substrate R^2	Yield **7** [%][b,c]	Yield **8** [%][b,c]
1	Me	H	90	54
2	Et	H	97	60
3[d]	$PhCH_2$	H	91	85
4	Me	Me	97	84
5	Me	Cl[e]	97	76
6	Me	Ph[f]	92	77
7[g]	 **6b**		80	51
8	 **6c**		–	48[h]
9[i]	 **6d**		–	61[h]

[a] Acetonides **6** (1.0 equiv) were cleaved with $TsOH \cdot H_2O$ (0.1 equiv) in MeOH (0.1 M) over 2–3 h unless otherwise noted. Diols **7** were oxidized with H_5IO_6 (1.5 equiv) in 2:1 $THF:H_2O$ (0.033 M) unless otherwise noted. TsOH = *p*-toluenesulfonic acid [b] Yields of isolated product. [c] There is no measurable change of *ee* value through this sequence. [d] Acetonide cleavage was performed in EtOH over 6 h. [e] Absolute stereochemistry has been assigned by analogy, except in this case, which was assigned by conversion into (+)-(*S*)-citramalic acid dimethyl ester.[12] [f] Direct treatment with H_5IO_6 and subsequent methylation provided the ester in 47% yield over two steps. [g] See the Supporting Information for a description of the preparation of **6b** from **6a** by cross-metathesis. [h] Three-step yield. [i] Oxidation performed with H_5IO_6 (1.0 equiv).

more,the tetrasubstituted dioxanone derivative **6** may incorporate enolizable α,β-unsaturated esters (Table 3, entry 7), or cyclic structures (Table 3, entries 8 and 9) as substituents.

Notably, assembly of acid (*S*)-**10** (see Scheme 2) constitutes a catalytic enantioselective formal synthesis of (−)-quinic acid (**1**),[14] a useful chiral building block that has been



Scheme 2. Formal synthesis of (−)-quinic acid (**1**) and (−)-dragmacidin F (**11**).

employed in numerous syntheses,[15] including our recent synthesis of dragmacidin F.[16] Toward this end, we recognize that enantioenriched α,ω-dienes can be transformed into cycloalkenes with a stereocenter remote to the olefin.[17] Chiral diene **6e** undergoes ring closing metathesis to generate 3-methylcyclopentene **6c** in 95% yield and 85% *ee*. Likewise, enantioenriched α,ω-diene **6f** furnishes cyclohexene **6d** in 90% yield and 92% *ee*. Cyclohexene **6d** readily undergoes acetonide cleavage and periodic acid oxidation to provide pure, isolable acid (*S*)-**10**, completing the formal synthesis of (−)-quinic acid (**1**).

In summary, we have developed a palladium-catalyzed asymmetric alkylation of simple dioxanone derivatives, and transformed the enantioenriched products into α-hydroxyketones, acids, and esters. This mild, straightforward sequence proceeds in high yield and enantioselectivity. This procedure has also enabled a catalytic enantioselective formal synthesis of (−)-quinic acid. Research is underway to extend this chemistry to other α-heteroatom-containing carbonyl derivatives and to employ these methods in the total synthesis of bioactive natural products.

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chromatography in 46–78% yield, with 6–15% yield of the isomeric enol ether. For details, see the Supporting Information.
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