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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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Abstract

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. These include quinic acid (**1**), cytotoxic leiodolide A (**2**),[2] and the anti-cancer 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]

Keywords

Alcohol; Allylic compounds; Asymmetric catalysis; Enantioselectivity; Palladium

For this application, we chose to incorporate oxygenation into a cyclic motif, the 2,2-dimethyldioxanone framework,[8] and employ this platform for the enantioselective synthesis of α-dialkyl ketones (e.g., **4**). Dioxanones are challenging alkylation substrates because standard conditions do not permit alkylation, but instead facilitate ketone reduction (e.g., LDA, −78 °C), or self-condensation (e.g., 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 (Figure 2, eq 1). We believed our catalytic palladium technology would be an ideal platform to provide access to valuable tetrasubstituted α-hydroxyketones, esters, and acids (Figure 2, eq 2).

We examined the conversion of silyl enol ether **4 a**[10] to enantioenriched tetrasubstituted ether **6a** under a variety of palladium-catalyzed conditions, beginning with the standard

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conditions developed for the all-carbon system (Table 1). 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%), (*S*)-*t*-BuPHOX (**5**, 5.5 mol%),[11] $Bu_4NPh_3SiF_2$ (TBAT, 1 equiv), and diallyl carbonate (1.05 equiv) in THF at 30 °C (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 $PhCH_3$ as solvent furnished dioxanone **6a** in 74% yield and 89% *ee* (entry 5).

We applied these 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 (entries 1 and 2), benzyl (entry 3), and alkenyl (entries 7–9) moieties. Additionally, the reaction proceeds when the allyl group is substituted internally by methyl, chloro, or phenyl (entries 4–7) to afford products in high yields and *ee*.

Having established a general route to enantioenriched tetrasubstituted dioxanones **6**, we have developed a straightforward sequence to transform these α-alkoxyketones into the corresponding α-hydroxyesters **8** (Table 3). To effect acetonide cleavage, enantioenriched products **6** are treated with catalytic *p* -toluenesulfonic acid in methanol or ethanol. Dihydroxyketones **7** are oxidatively cleaved in the presence of periodic acid, selectively removing the primary alcohol,[13] to generate α-hydroxyacids. Subsequent methylation furnishes tetrasubstituted enantioenriched α-hydroxyesters **8**. These operations are tolerant of a number of substitutents including alkyl (entries 1–4), chloro (entry 5), and aryl (entries 3 and 6) groups. Furthermore, dioxanone derivatives may include enolizable α,β-unsaturated esters (entry 7), or be incorporated into cyclic structures (entries 8 and 9).

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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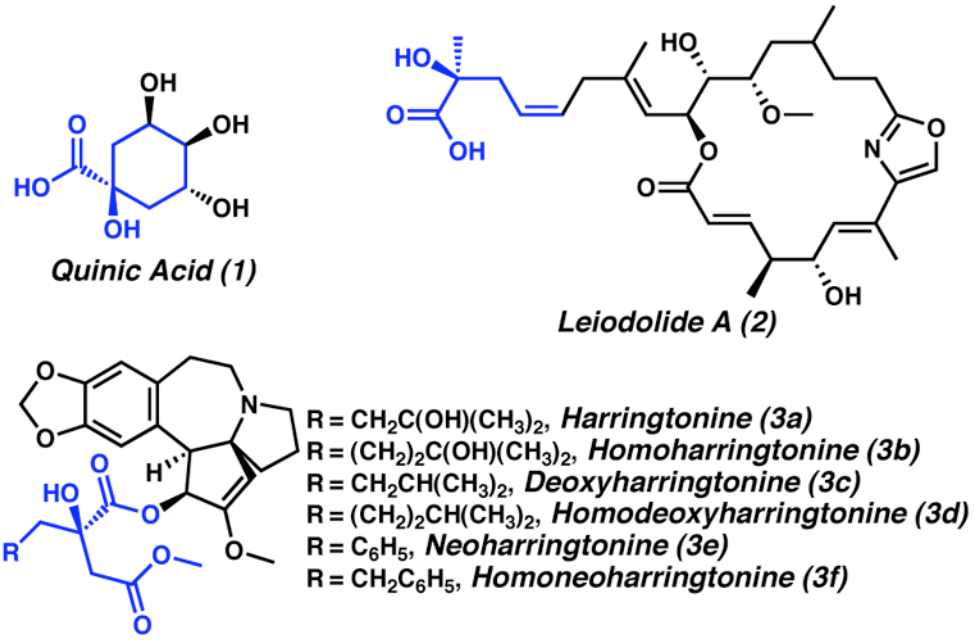


Figure 1.
Natural products containing α-hydroxyesters and acids.

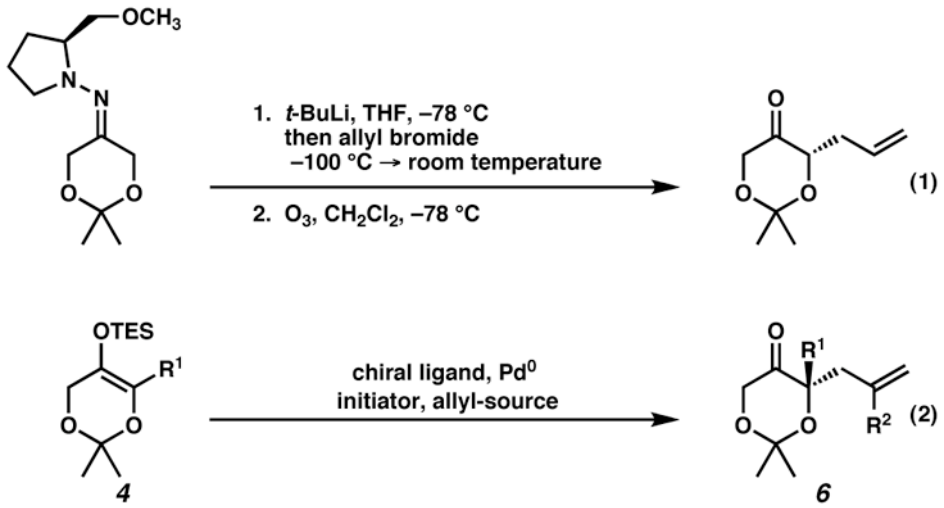
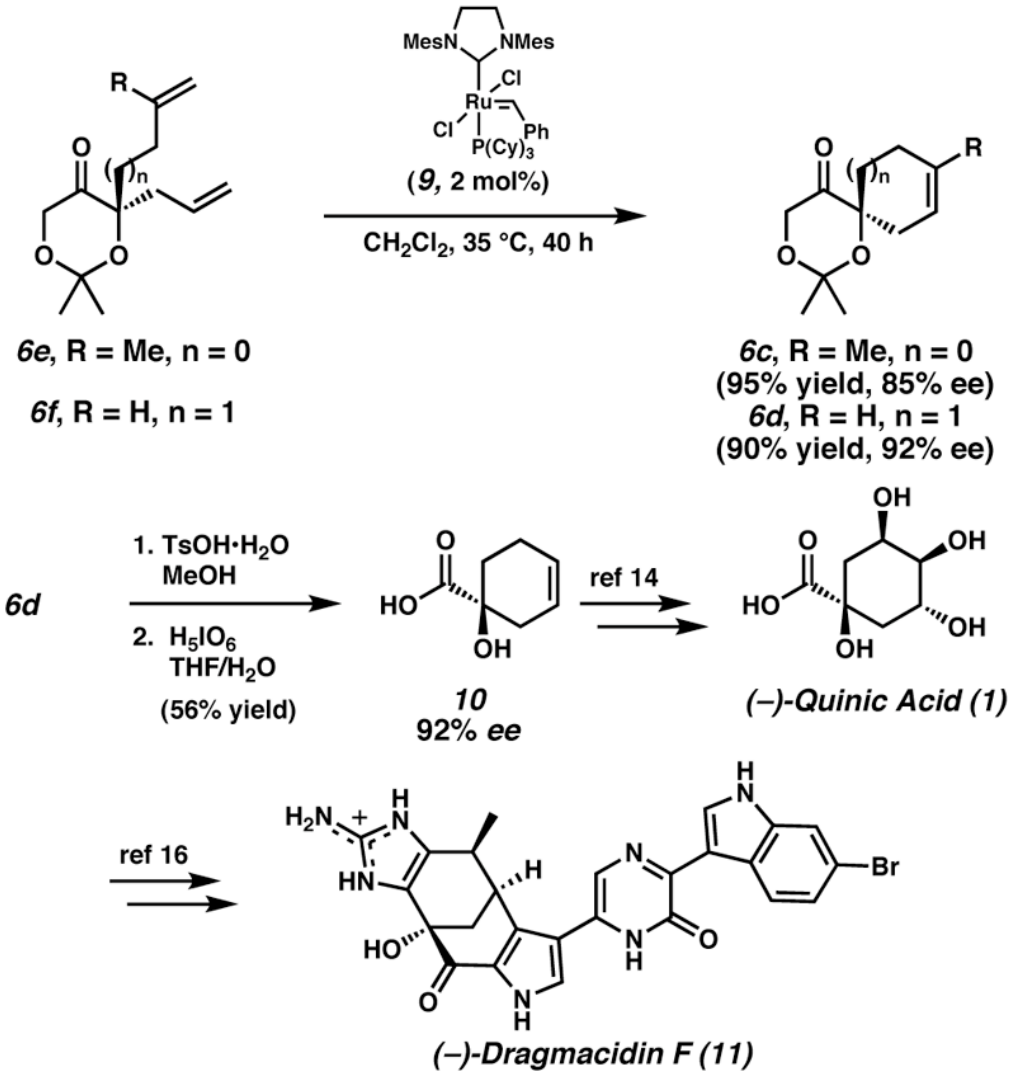


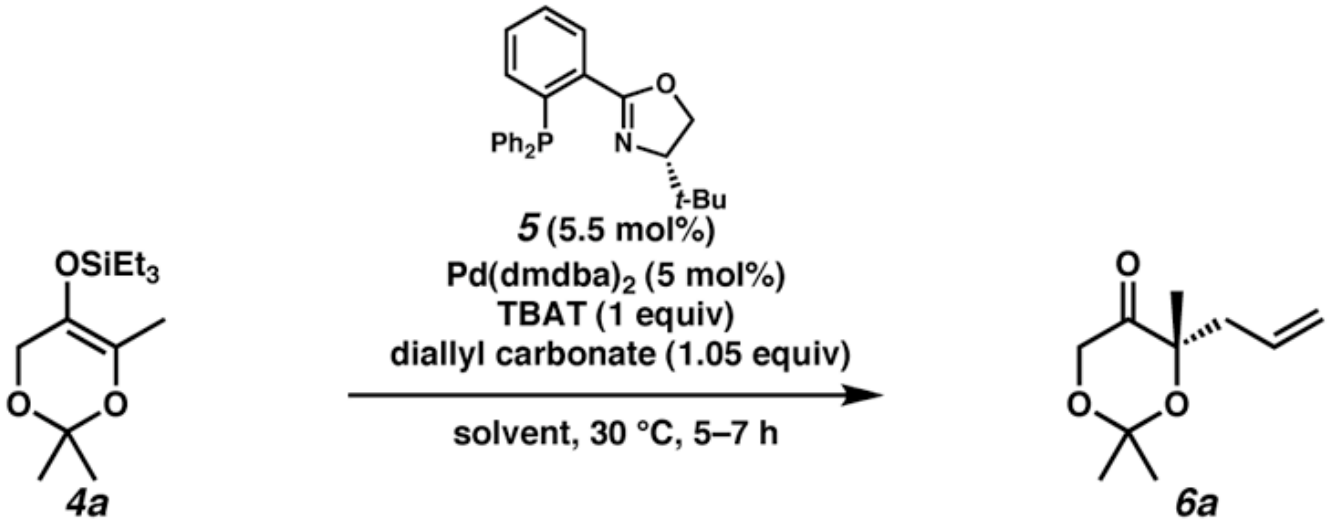
Figure 2.
Alkylation technologies using the dioxanone framework.



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

Table 1

Optimization of the enantioselective enol silane allylation.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	THF	40	81
2[d]	Et_2O	59	89
3	1,4-dioxane	65	67
4	PhH	67	84
5	$PhCH_3$	74	89

[a] Reactions were performed using 0.1 mmol of substrate in solvent (0.033 M) at 30 °C over 5–7 h unless stated otherwise.

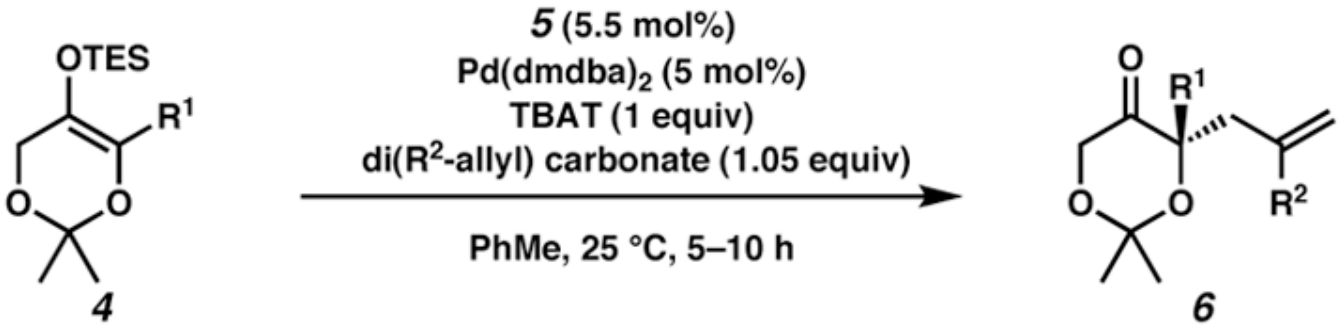
[b] Isolated yields.

[c] Measured by chiral HPLC following conversion to **6b**.[12]

[d] Performed at 35 °C and 0.0167 M. dmdba = bis(3,5-dimethoxybenzylidene)acetone

Table 2

Substrate scope for the enantioselective alkylation.[a]



Entry	R^1	R^2	Yield [%][c]	*ee* [%][d]
1	Me	H	86	87
2	Et	H	79	93
3	$PhCH_2$	H	85	86
4[e, f]	Me	Me	59	89
5[g]	Me	Cl[b]	59	92
6[h]	Me	Ph	73	94
7[f]	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] Absolute stereochemistry has been assigned by analogy, except in the case of **6c**, which was assigned by conversion to (+)-(*S*)-citramalic acid dimethyl ester.[12]

[c] Isolated yields.

[d] Measured by chiral GC or HPLC.[12]

[e] Performed with trimethylsilyl precursor, 35 mol% TBAT in Et_2O (0.0167 M) at 25 °C.

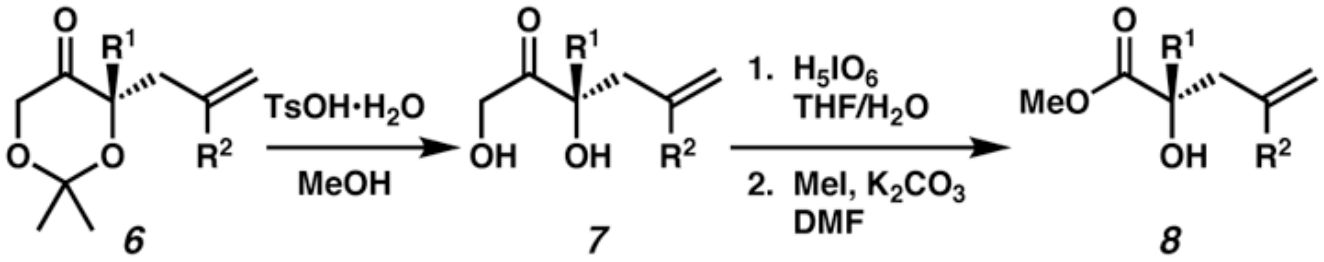
[f] Performed with dimethallyl carbonate (1.05 equiv).

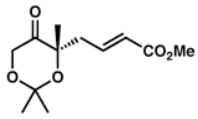
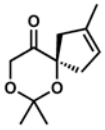
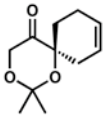
[g] Performed with dichloroallyl carbonate (1.05 equiv) at 35°C.

[h] Performed with diphenylallyl carbonate (1.05 equiv).

Table 3

Substrate scope for methyl ester formation.[a]



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

[a] Acetonides **6** (1.0 equiv) were cleaved with TsOH•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.

[b] Absolute stereochemistry has been assigned by analogy, except in this case, which was assigned by conversion to (+)-(*S*)-citramalic acid dimethyl ester.[12]

[c] Isolated yields.

[d] There is no measurable change of *ee* through this sequence.

[e] Acetonide cleavage was performed in EtOH over 6 h.

[f] Three step yield.

[g] Oxidation performed with H_5IO_6 (1.0 equiv).

[h] Direct treatment with H_5IO_6, and methylation provided the ester in 47% yield over two steps.

[i] See the supporting information for a description of the preparation of **6 b** from **6a** via cross-metathesis. TsOH = *p*-toluenesulfonic acid