Synthetic Methods

DOI: 10.1002/ange.201203663

Enantioselective Synthesis of Tertiary α-Hydroxyketones from Unfunctionalized Ketones: Palladium-Catalyzed Asymmetric Allylic Alkylation of Enolates**

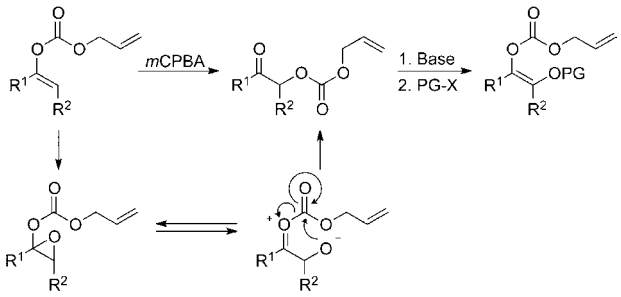
Barry M. Trost, Raffael Koller, and Benjamin Schäffner*

Tertiary α-hydroxyketones are found in many biologically active compounds. These include the phytolexin lacineline C and the homoisoflavanone eucomol, both of which have a tetralone ring system.

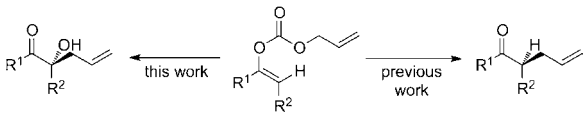
Despite their presence in a variety of biologically active targets, only a few catalytic methods are known to generate this functionality in an enantioselective fashion. Phase-transfer-catalyzed oxidations of simple ketones using molecular oxygen have been reported.[1] However, in general, these methods require high catalyst loadings and only moderate enantioselectivities are obtained. Suzuki and co-workers developed an intramolecular crossed aldehyde–ketone benzoin cyclization with chiral triazolium salts as catalysts to access tertiary α-hydroxyketones in moderate to excellent yield and enantiomeric excess, but this strategy required high catalyst loadings (10–20 mol%).[2] Sharpless and co-workers reported the osmium-catalyzed dihydroxylation of cyclic silyl enol ethers to give tertiary α-hydroxyketones.[3] However, slight structural variation in the substrates resulted in large changes in the enantioselectivity using this method.

Previously, we reported palladium-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) of enolcarbonates to access both tertiary and quaternary stereocenters.[4] To demonstrate the power of this transformation, we envisioned the oxidation of the enol carbonate, such that an additional oxygen functionality was present, for use as substrates in the Pd-DAAA to access highly oxygenated chiral products.

We envisaged that simple, readily accessible allyl enol carbonates[5] could be chemoselectively oxidized to yield the corresponding keto carbonates. Oxidation using *m*-CPBA should initially yield the corresponding epoxides, which could rearrange to give the more stable keto carbonates (Scheme 1). To our surprise, such an oxidation/rearrangement protocol was unprecedented in the literature. In a second step, these substrates could be enolized and protected to give the



Scheme 1. Synthesis of 1,2-endiol carbonates from simple enol carbonates. *m*CPBA = *meta*-chloroperbenzoic acid, PG = protecting group.



Scheme 2. Pd-DAAA for the synthesis of tertiary α-hydroxyketones.

desired substrates for the Pd-DAAA reaction as shown in Scheme 2.

As model substrates, tetralones and benzosuberones were chosen. The corresponding enol allyl carbonates were synthesized by selective O-acylation using allyl imidazole carboxylate along with boron trifluoride etherate, a high yielding method previously reported by our group (Table 1).[5]

Epoxidation of the enolcarbonates was achieved using *m*-CPBA in CH_2Cl_2 at room temperature (Scheme 3). For the encolcarbonates **2a–f**, which are derived from tetralones, full conversion was observed after one hour. The reactions of the benzosuberone-derived substrates **2g** and **2h** were somewhat slower and the reaction was stopped after two hours at room temperature. The resulting epoxides are surprisingly stable even under aqueous conditions. The epoxide opening was facilitated by using $BF_3{\cdot}OEt_2$ as the Lewis acid in Et_2O. Under the described reaction conditions complete acyl migration was observed.

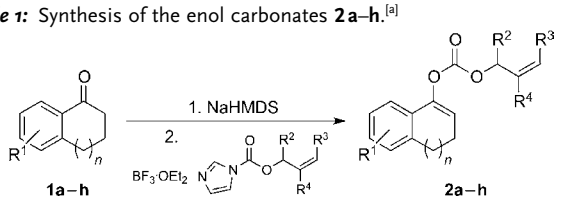
Upon deprotonation of **4a–h** with NaHMDS, the resulting enolates undergo complete acyl migration to form the thermodynamically favored regioisomer even at −78 °C. The enolate was then treated with MOMI, thus yielding the MOM-protected 1,2-endiol carbonate (Scheme 4). Similarly, the enolate could be treated with BOMI,[6] thus affording the protected carbonate. Both the MOM- and BOM-protected 1,2-endiol carbonates were obtained in good to excellent yield. The carbonates **5a–l** are stable and can be stored for

[*] Prof.Prof. B. M. Trost, Dr. R. Koller, Dr. B. Schäffner
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
E-mail: bmtrost@stanford.edu
Homepage: http://www.stanford.edu/group/bmtrost

[**] We thank the NSF (CHE 0948222) for their generous support of our programs. R.K. acknowledges support from the Schweizerische Nationalfonds (SNF); B.S. is grateful to the Alexander von Humboldt Foundation for a Feodor Lynen Fellowship.

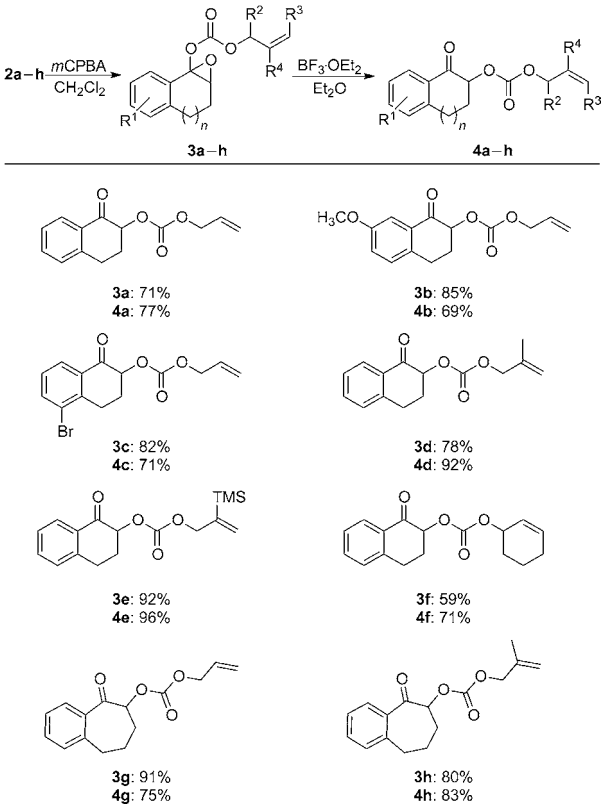
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201203663.

Table 1: Synthesis of the enol carbonates **2a–h**.[a]



Entry	2	R^1	R^2	R^3	R^4	*n*	Yield [%][b]
1	**2a**	H	H	H	H	1	88
2	**2b**	7-OCH_3	H	H	H	1	97
3	**2c**	5-Br	H	H	H	1	91
4	**2d**	H	H	H	CH_3	1	99
5	**2e**	H	H	H	TMS	1	84
6	**2f**	H	-$CH_2CH_2CH_2$-		H	1	80
7	**2g**	H	H	H	H	2	74
8	**2h**	H	H	H	CH_3	2	86

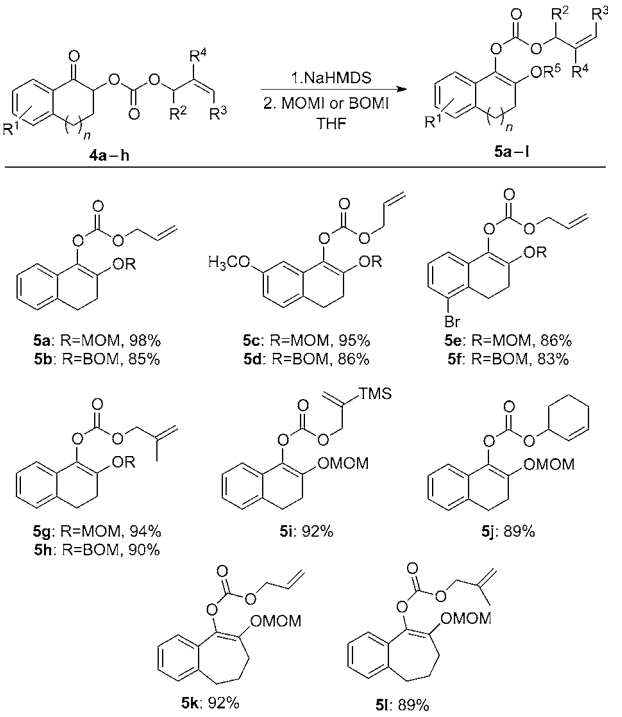
[a] Reaction conditions: **1** (1.00 equiv), NaHMDS (1.20 equiv), allyl imidazole carboxylate (1.20 equiv), $BF_3{\cdot}OEt_2$ (1.20 equiv) in DME at −78 °C for 1 h. [b] Yields refer to yields of isolated product. DME = dimethoxyethane, HMDS = hexamethyldisilamide, TMS = trimethylsilyl.



Scheme 3. Epoxidation and subsequent ring opening. Reaction conditions for the synthesis of **3a–h**: **2a–h** (1.00 equiv), *m*CPBA (1.50 equiv) in CH_2Cl_2 (1.20 equiv) at RT for 1–2 h. Reaction conditions for the synthesis of **4a–h**: **3a–h** (1.00 equiv), $BF_3{\cdot}OEt_2$ (1.00 equiv) in Et_2O at −78 °C for 1 h. Yields refer to yields of isolated product.

weeks and even up to several months at low temperatures, if protected from moisture.

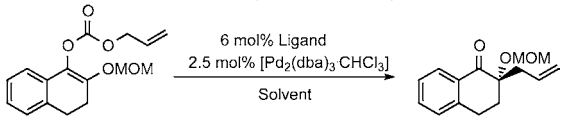
The 1,2-endiol carbonate **5a** was chosen for optimization studies (Table 2) and subjected to the Pd-DAAA using the standard dppba ligands (Figure 1) developed in our group. Initial optimization studies were conducted in THF. The best



Scheme 4. Synthesis of the protected 1,2-endiol carbonates. Reaction conditions for the synthesis MOM-protected **5**: **4a–h** (1.00 equiv), NaHMDS (1.20 equiv), MOMI (1.20 equiv) in THF at −78 °C. Reaction conditions for the synthesis BOM protected **5**: **4a–d** (1.00 equiv), NaHMDS (1.20 equiv), $(BnO)_2CH_2$ (1.60 equiv), TMSI (1.50 equiv) in THF at −78 °C. Yields refer to yields of isolated product. BOM = benzyloxymethyl, MOM = methoxymethyl, THF = tetrahydrofuran.

results in terms of enantioselectivity, were obtained with the anthracenyl-diamine-derived ligand (*R*,*R*)-**L4** (Table 2, entries 1–4). Full conversion of the starting material **5a** was observed after 12 hours at room temperature. The product could be isolated with an enantiomeric excess of 96 %. (*R*,*R*)-**L1** and (*R*,*R*)-**L3** showed a higher reactivity albeit with lower enantiodiscrimination. Screening of different solvents revealed that the initially used THF was the solvent of

Table 2: Selected results for the palladium-catalyzed DAAA of **5a**.[a]



Entry	Solvent	Ligand	Conversion [%][b]	*ee* [%]
1	THF	(*R*,*R*)-**L1**	>99	71
2	THF	(*R*,*R*)-**L2**	17	60
3	THF	(*R*,*R*)-**L3**	>99	42
4	**THF**	(*R*,*R*)-**L4**	**>99**	**96**
5	DME	(*R*,*R*)-**L4**	>99	88
6	1,2-DCE	(*R*,*R*)-**L4**	29	75
7	1,4-dioxane	(*R*,*R*)-**L4**	>99	93

[a] Reaction conditions: **5a** (1.00 equiv), [Pd2(dba)3·CHCl3] (2.5 mol %), Ligand (6 mol %) in the indicated solvent (0.1 M in **5a**) at RT for 16 h. [b] Determined by ^1H NMR. dba = dibenzylideneacetone, DCE = dichloroethane.

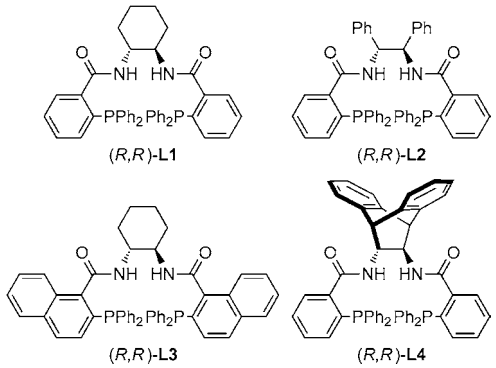
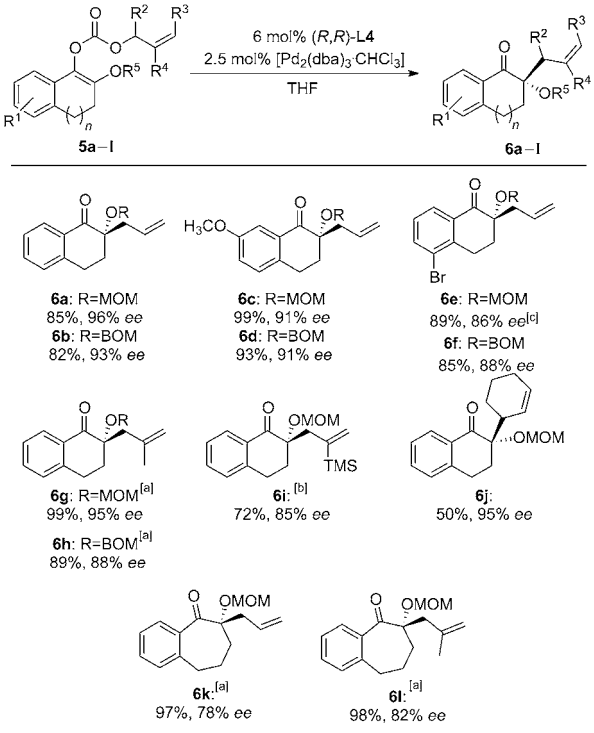


Figure 1. The most commonly used dppba ligands **L1**–**L4**.

choice even though 1,4-dioxane gave comparable results to that of THF (Table 2, entry 7). The absolute stereochemistry is assigned by analogy to the DAAA of 2-substituted tetralones and benzsuberones.

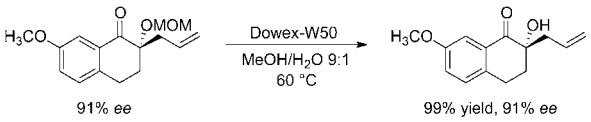
With the optimized reaction conditions in hand, a variety of 1,2-endiol carbonates were subjected to Pd-DAAA (Scheme 5). In general, good to excellent yields and enantioselectivities were obtained. We were pleased to see that the BOM-protected **5b** gave a comparable enantioselectivity to **5a**, that is, 93% compared to 96%. Tolerance of both MOM and BOM groups allows several protecting group strategies, which is advantageous in synthesis. A similar observation was made for the yield of the reaction (82% compared to 85%).



Scheme 5. Pd-DAAA of 1,2-endiol carbonates **5a–l** in THF. [a] Reaction conditions for the Pd-DAAA: **5a–l** (1.00 equiv), $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5 mol%), (*R*,*R*)-**L4** (6 mol%) in THF (0.1 M in **5a–l**) at RT for 16 h. Yields refer to yields of isolated product. [a] (*R*,*R*)-**L3** was used at 45 °C. [b] (*R*,*R*)-**L1** was used at 45 °C. [c] Determined after hydrolysis to the free alcohol.

Electron-rich substrates gave excellent yields (93% to 99%) with slightly lower enantioselectivities in the range of 90%. The brominated tetralones **6e** and **6f** were obtained in a slightly lower yield. However, no dehalogenation product was observed. These compounds are attractive starting materials which can be derivatized using cross-coupling chemistry. The reaction also tolerates substituents on the allyl moiety. For the sterically more demanding substrates **5g** and **5h**, the more reactive ligand (*R*,*R*)-**L3** along with a slightly elevated reaction temperature (45 °C) were used to give excellent yields and enantioselectivities. For the sterically even more demanding carbonate **5i**, the ligand (*R*,*R*)-**L1** was used to give the desired product in 72% yield and 85% *ee*. Variation of the allyl moiety to cyclohexenyl gave the desired ketone **6j** in excellent enantiomeric excess as a single diastereoisomer, albeit in only 50% yield. Interestingly, as a side product, the *O*-allylated product was obtained in 34% yield and 65% *ee*. These numbers can be explained by the steric demand of both the nucleo- and the electrophile upon oxidative addition which leads to allylation at the oxygen atom, which is sterically less demanding. The benzosuberone-derived substrates **5k** and **5l** gave the best results with (*R*,*R*)-**L3**.

As shown for **6c** in Scheme 6, the MOM-protected hydroxylketones can easily be deprotected under relatively mild reaction conditions using a cationic exchange resin



Scheme 6. Deprotection of **6c** using a cationic exchange resin.

(Dowex-50W) in aqueous methanol, a method reported by Seto et al.[7] The resulting hydroxyketone was obtained in excellent purity without need for further purification after filtration through silica.

To conclude, we have demonstrated a highly region- and enantioselective palladium-catalyzed decarboxylative asymmetric allylic alkylation to access highly functionalized tertiary α-hydroxyketones from simple ketones. The starting materials for the reaction were accessed using an unprecedented chemoselective epoxidation of enolcarbonates with a subsequent Lewis acid mediated ring opening. We are currently investigating the extension of this methodology to acyclic substrates.

Experimental Section

General Procedure for the Pd-DAAA: Freshly distilled and degassed THF (0.5 mL) was added to the ligand (*R*,*R*)-**L1**, (*R*,*R*)-**L2**, or (*R*,*R*)-**L4** (0.006 mmol, 6 mol%) and $[Pd_2(dba)_3{\cdot}CHCl_3]$ (0.0025 mmol, 2.5 mol%) under Ar. The resulting suspension was stirred at 45 °C until a clear, bright-orange color was obtained, and it was then cooled to RT. The catalyst solution was then added to the substrate **5** (0.10 mmol, 1.00 equiv) under Ar in freshly distilled and degassed THF (0.5 mL). The reaction turns yellow immediately and is then stirred for 16 h at the given temperature. After full conversion the

reaction turns bright orange, thus indicating the presence of the Pd^0/phosphine complex. The solution was concentrated and purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give the desired protected hydroxy ketone.

Received: May 11, 2012
Published online: July 24, 2012

Keywords: alcohols · allylic compounds · asymmetric catalysis · ketones · palladium

[1] M. Masui, A. Ando, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 2835; E. V. Dehmlow, V. Knufinke, *Liebigs Ann. Chem.* **1992**, 283; E. V. Dehmlow, M. Romero, *J. Chem. Res.* **1992**, 400; E. F. J. de Vries, L. Ploeg, M. Colao, J. Brussee, A. van der Gen, *Tetrahedron: Asymmetry* **1995**, *6*, 1123.

[2] H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.

[3] K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 8463.

[4] B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846; B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180; B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282; B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11852; B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343; B. M. Trost, K. Lehr, D. J. Michaelis, J. Xu, A. K. Buckl, *J. Am. Chem. Soc.* **2010**, *132*, 8915; B. M. Trost, B. Schäffner, M. Osipov, D. A. A. Wilton, *Angew. Chem.* **2011**, *123*, 3610; *Angew. Chem. Int. Ed.* **2011**, *50*, 3548; B. M. Trost, D. J. Michaelis, J. Charpentier, J. Xu, *Angew. Chem.* **2012**, *124*, 208; *Angew. Chem. Int. Ed.* **2012**, *51*, 204.

[5] B. M. Trost, J. Xu, *J. Org. Chem.* **2007**, *72*, 9372.

[6] BOMI was prepared prior to its use from $(BnO)_2CH_2$ and TMSI; for additional information see the Supporting Information.

[7] H. Seto, L. N. Mander, *Synth. Commun.* **1992**, *22*, 2823.

