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The Enantioselective Tsuji Allylation

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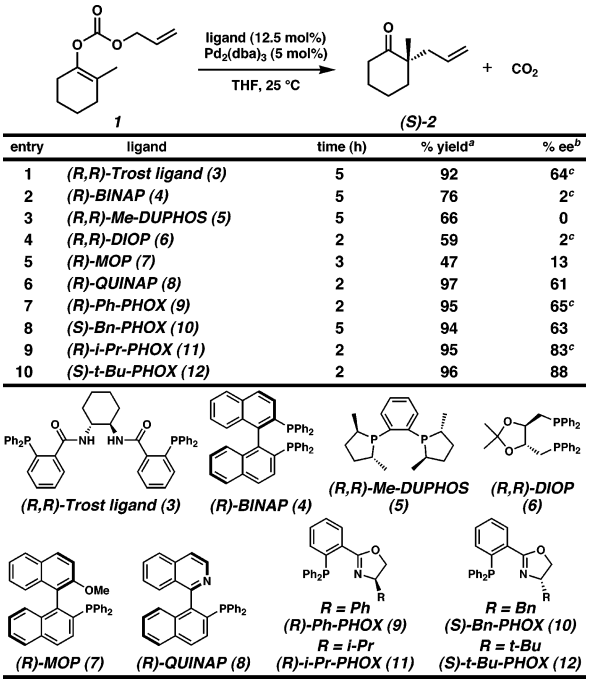
Palladium-catalyzed enantioselective allylation chemistry has played a critical role in the evolution of asymmetric catalysis as a field.[1] Developments in the area of asymmetric C−C bond formation by these methods over the past two decades by Trost, Helmchen, Pfaltz, and others have been focused primarily on the direct allylation of malonates by prochiral electrophiles.[1] In general, reactions involving prochiral nucleophiles are rare; however, examples using activated dicarbonyl compounds[2] and carbonyl compounds that can only form a single enolate under the base-mediated reaction conditions (e.g., tetralones) have recently been reported.[3] Due to these constraints, there are no enantioenriched examples of even the simplest 2-methyl-2-allyl cyclohexanone (i.e., **2**) in the literature. In the course of a total synthesis investigation, we became interested in such α-quaternary cycloalkanones and initiated an effort to prepare them in a catalytic asymmetric fashion.[4] Moreover, the potential broad utility of such chiral building blocks warranted investigation. Herein, we present the first examples of the asymmetric Tsuji allyl enol carbonate[5] and silyl enol ether allylations,[6] which provide unprecedented access to these important cyclohexanones in a highly enantioenriched form.

Of the numerous examples of palladium-catalyzed allylic alkylations, we became interested in the decarboxylative alkylation of allyl enol carbonates to the corresponding α-allylcyclohexanone derivatives described by Tsuji (i.e., **1** → **2**, ligand = PPh_3).[5] Despite the power of this reaction to build quaternary carbon centers under essentially neutral conditions, it has seen limited use in the 20 years since its discovery.[4,7] Our analysis revealed the Tsuji allylation to be an ideal reaction for the synthesis of asymmetric α-quaternary cycloalkanones because the selective formation of the enol carbonate moiety provides position control of the enolate and, thereby, the product.[5b,8] Therefore, we initiated an effort to promote the asymmetric Tsuji allylation of enol carbonate **1** under palladium catalysis.

We examined the transformation of enol carbonate **1** to allyl ketone **2** using a variety of chiral ligands (12.5 mol %) and $Pd_2(dba)_3$ (5 mol %) in THF at 25 °C.[9] As shown in Table 1, palladium catalysts derived from C_2-symmetric (bis)phosphines (i.e., **3**−**6**) and mixed P/O ligands (e.g., **7**) displayed good reactivity but produced ketone **2** in low to modest enantiopurity (entries 1−5). Interestingly, mixed P/N-type ligands were more effective at inducing asymmetry (entries 6−10).[10] In particular, the phosphinooxazolines (PHOX) **9**−**12**[11] induced high degrees of enantioselectivity and reactivity in the allylation (entries 7−10). In the ideal case, the use of the (*S*)-*t*-Bu-PHOX ligand **12** provided cyclohexanone (*S*)-**2**[12] in 96% yield and 88% ee (entry 10). As a final refinement, reactions could be performed reliably using 6.25 mol % ligand **12** and 2.5 mol % $Pd_2(dba)_3$ (Table 2).

We applied these optimized conditions to the allyl enol carbonates of a variety of substituted cyclic ketones (Table 2). The asymmetric allylic alkylation tolerates a range of substitution at the 2-position of the cyclohexenyl portion of the enol carbonate (entries 1−7). Additionally, a 2-methallylated product can be generated from the corresponding 2′-methyl allyl carbonate (entry 8). Furthermore, the ring portion of the cyclic enol carbonate can

Table 1. Ligand Screen



entry	ligand	time (h)	% yield[a]	% ee[b]
1	*(R,R)-Trost ligand (3)*	5	92	64[c]
2	*(R)-BINAP (4)*	5	76	2[c]
3	*(R,R)-Me-DUPHOS (5)*	5	66	0
4	*(R,R)-DIOP (6)*	2	59	2[c]
5	*(R)-MOP (7)*	3	47	13
6	*(R)-QUINAP (8)*	2	97	61
7	*(R)-Ph-PHOX (9)*	2	95	65[c]
8	*(S)-Bn-PHOX (10)*	5	94	63
9	*(R)-i-Pr-PHOX (11)*	2	95	83[c]
10	*(S)-t-Bu-PHOX (12)*	2	96	88

[a] GC yield relative to an internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC (ref 14). [c] (*R*)-**2** produced as the major product (ref 12).

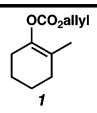
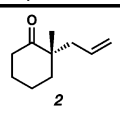
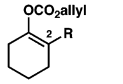
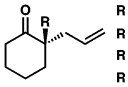
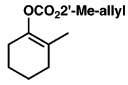
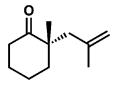
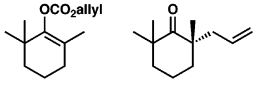
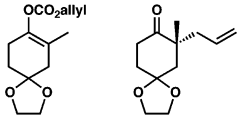
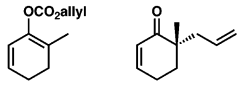
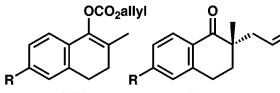
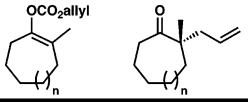
be substituted (entries 9 and 10) and unsaturated (entries 11−13) in various ways. Gratifyingly, the allylation can be applied to seven- and eight-membered rings (entries 14 and 15) in addition to cyclohexanones.[13] We have also demonstrated that **2** can be obtained in near enantiopurity (96% ee) after a single crystallization of the corresponding semicarbazone (entry 2).[14] Importantly, all of the products displayed in Table 2 possess a catalytically generated asymmetric quaternary carbon center and, with the exception of the tetralone examples (entries 12 and 13), were previously unknown as enantioenriched entities, despite their apparent simplicity.

Having successfully prepared a range of α-quaternary cycloalkanones in high enantiomeric purity via the corresponding enol carbonates, we investigated the possibility of using simple enol ethers as the nucleophilic component (Table 3).[6] To our delight, a range of tetrasubstituted trimethylsilyl enol ethers underwent smooth α-allylation using commercially available diallyl carbonates as electrophiles. Again, we observed high yields and enantioselectivities for the production of an array of α-quaternary cycloalkanones using the $Pd_2(dba)_3$/**12**-derived catalyst and a substoichiometric amount of $Bu_4NPh_3SiF_2$ (TBAT) to serve as an initiator. The allylation of silyl enol ethers complements the enol carbonate chemistry as the preparation of the former is often more convenient.[14]

To display the utility of these α-quaternary cyclic ketones, we carried out a number of straightforward synthetic transformations on the parent 2-allyl-2-methyl cyclohexanone (Scheme 1). Namely,

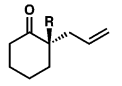
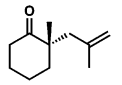
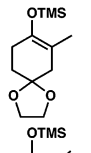
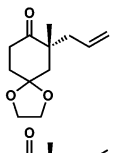
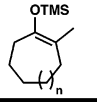
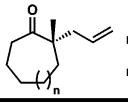
10.1021/ja044812x CCC: $27.50

Table 2. Enantioselective Tsuji Enol Carbonate Allylation[a]

entry	substrate	product		time (h)	% yield[b]	% ee[c]
1				2	85	87
2[d]				5	85	88 (96)[e]
3[f]				9	90	89
4			R = CH_2CH_3	2	96	92
5[g]			R = *t*-Bu	10	55[h]	82
6			R = CH_2Ph	2	96	85
7			R = $(CH_2)_3OBn$	2	87	88
8[g]				8	89	91
9				1	94	92
10				1	87	86
11				1	91	89
12[i]			R = H	2	87	91
13[i]			R = OCH_3	8	94	91
14			n = 1	6	81	87
15			n = 2	2	90	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C, with $Pd_2(dba)_3$ (2.5 mol %) and **12** (6.25 mol %), unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC (ref 14). [d] Performed on a 5.1 mmol scale. [e] In parentheses, is the % ee after one recrystallization of the corresponding semicarbazone (ref 14). [f] Reaction performed at 12 °C (GC yield). [g] Performed with 5 mol % $Pd_2(dba)_3$ and 12.5 mol % **12**. [h] Isolated yield after conversion to the corresponding diketone via Wacker oxidation (ref 14). [i] Performed at 10 °C.

Table 3. Enantioselective Tsuji Enol Silane Allylation[a]

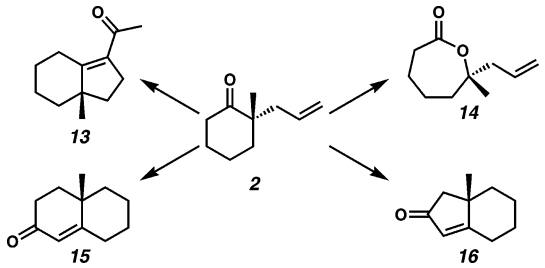
entry	substrate	product		time (h)	% yield[b]	% ee[c]
1			R = CH_3	2	95	87
2			R = CH_2CH_3	3	96	92
3[d]				4	79	91
4				2	99	81
5			n = 1	2	94	86
6			n = 2	3	96	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C, with $Pd_2(dba)_3$ (2.5 mol %), **12** (6.25 mol %), diallyl carbonate (1.05 equiv), and TBAT (35 mol %), unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC (ref 14). [d] Reaction performed with dimethallyl carbonate (1.05 equiv).

ketone (*S*)-**2** (98% ee) was converted to products **13**−**16** by standard methods.[14] These representative transformations illustrate the potential versatility and importance of allyl cycloalkanones as chiral building blocks in synthesis.

In summary, we have developed the first catalytic enantioselective Tsuji allylations of simple alkanone derivatives. These mild, operationally straightforward, and stereoselective reactions produce chiral cycloalkanones with quaternary stereocenters at the α-position

Scheme 1 [a]



[a] From ref 14.

in high enantiopurity and excellent chemical yield. Investigation of this chemistry in other settings is currently being explored.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For recent reviews on the catalytic enantioselective generation of quaternary stereocenters, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(5) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140−145. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793−1796. (c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523−1529.

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(7) For examples of Tsuji enol carbonate allylations in synthesis, see: (a) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755−767. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482−2486. (c) Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem.* **1993**, *58*, 678−682.

(8) Such enolate position control has not been achieved using direct in situ protocols.[1−3] Interestingly, the almost-exclusive existence of direct allylations contrasts developments in the area of asymmetric aldol chemistry, where enolate preactivation is usually required and, until recently, direct reactions were the exception.

(9) In addition to THF, a range of solvents, including dioxane,[5,6] PhH, $PhCH_3$, Et_2O, *tert*-butyl methyl ether, diisopropyl ether, and EtOAc could be used in the tranformation with little change in reactivity and selectivity.

(10) For a recent review of chiral mixed P/N ligands for asymmetric catalysis, see: Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537.

(11) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (b) Williams, J. M. J. *Synlett* **1996**, 705−710 and references therein.

(12) The absolute configuration of (*S*)-**2** has been established by X-ray analysis of the derived crystalline (isopinocampheylamine) semicarbazone.[14] The absolute stereochemistry of the product in Table 2, entry 12, is known.[3] The absolute configuration shown for all other compounds is by analogy to these examples.

(13) Application of this methodology to cyclopentanone derivatives has, to date, resulted in modest enantioselectivities.

(14) See Supporting Information for details.

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