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Communication

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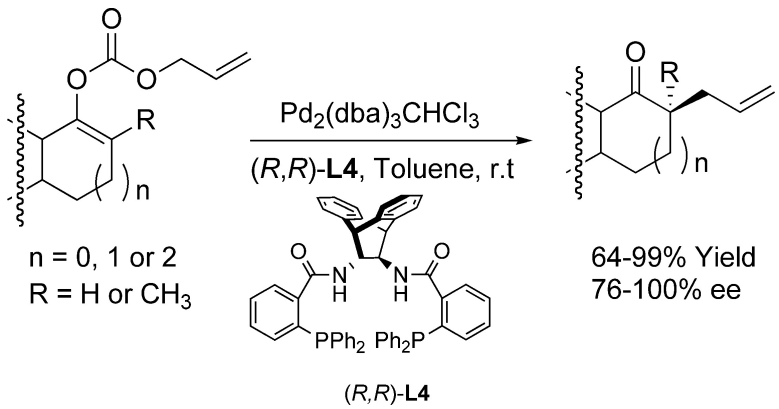


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# Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation of Ketones through Allyl Enol Carbonates

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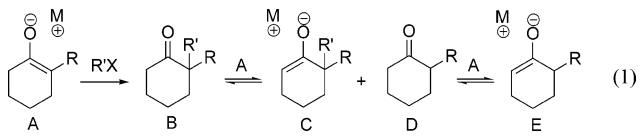
The asymmetric alkylation of unstabilized ketone enolates represents one of the most challenging reactions for asymmetric catalysis. A chiral auxiliary approach, most notably SAMP/RAMP, has shown the broadest generality.[1] Using chiral coordinating agents for metal cations, specifically lithium, in a catalytic fashion has been demonstrated, but its scope remains untested.[2] Our success with asymmetric allylic alkylation with ketone substrates for which only one enolate is possible[3] or one is strongly preferred[4] and in which a quaternary center is generated stimulated us to consider the prospect of using this strategy for unbiased ketones enolates.[5] Because these metal-catalyzed allylic alkylations are slow, enolate equilibration which can lead to both loss of regioselectivity (via **E**) as well as polyalkylation (via **C**) becomes competitive with alkylation of the initial enolate **A** as shown in eq 1. Furthermore, in the case where R = H in **A**, the chiral product **B** (R = H) is subject to racemization under these reactions conditions. A process wherein enolate alkylation could be performed under neutral conditions and wherein the concentration of enolate was low at any given moment might resolve both problems and allow regio- and enantioselective alkylation to create quaternary stereogenic centers but also enantioselective alkylation to create tertiary stereogenic centers with minimal product racemization. In this communication, we report the realization of these goals.[6]

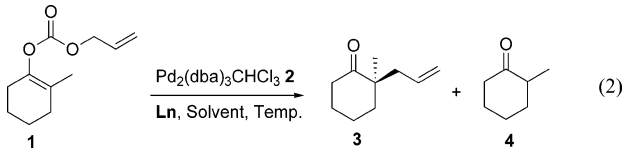



(1)

Initial studies examined the reaction of allyl 2-methylcyclohex-1-enyl carbonate **1** catalyzed by $Pd_2(dba)_3CHCl_3$ **2**[7] and ligand **L1** in DME (eq 2 and Table 1).[8] The reaction went to completion in 4 h at ambient temperature and led to alkylated product **3** in 81% yield and 66% ee. The only byproduct detected by GC is ketone **4** in 8% yield. The reaction was optimized by varying ligand, solvent, and temperature. Of these, ligand plays the most important role in terms of yield, ee, and reaction speed. Among the four ligands we had screened, **L4** gave the best ee and yield. The choice of solvent had a significant effect on the yield and ee of the reaction when we used **L1**, **L2**, or **L3**, while it had a smaller effect on the ee of the reaction when we used **L4**. The reaction is quite sensitive to water. As little as 1% $H_2O$ in DME caused the yield of **3** to decrease from 87% to 1.5 or 20% (Table 1, entries 2 and 9 vs entries 12 and 11). DME, THF, $CH_2Cl_2$, toluene, dioxane, acetonitrile, and DMSO were all examined with the least polar solvent, toluene, giving the best results. Figure 1 shows the chiral ligands used in the optimization studies.

These conditions were applied to a range of enol carbonates[9] and showed excellent enantioselectivity in creating quaternary centers (Table 2, entries 2−6). The ee's of entries 3 and 4 compare with 6 and 38% using tin enolates.[10] Interestingly, the absolute configuration of the product **12** using (*R*,*R*)-**L4** as the ligand is opposite to that obtained using the lithium enolate in the Pd asymmetric allylic alkylation (AAA).[3] Under the latter conditions, (*S*,*S*)-**L1** gave *R*-**12** in 85% ee. The complementary enantioselectivity by switching from the lithium enolate to enol carbonate wherein Pd must be the enolate counterion raises the prospect that the mechanism of the two processes, such as an outer sphere alkylation event in the former case versus an inner sphere one in the latter, might be different.

***Table 1.*** Selected Optimization Studies for Alkylation at Tertiary Carbon[a]




(2)

| entry | ligand | solvent | ee[b] | yield[c] of **3** | yield[c] of **4** |
|---|---|---|---|---|---|
| 1 | **L1** | DME | 66 | 81 | 8 |
| 2 | **L3** | DME | 76 | 87 | 2 |
| 3 | **L1** | toluene | 31 | 73 | 0 |
| 4 | **L2** | toluene | 61 | 73 | 2 |
| 5 | **L3** | toluene | 60 | 85 | 1 |
| 6 | **L4** | toluene | 85 | 88 | 0 |
| 7 | **L4** | $CH_2Cl_2$ | 84 | 64 | 26 |
| 8 | **L4** | dioxane | 80 | 99 | 0 |
| 9 | **L4** | DME | 84 | 87 | 7 |
| 10 | **L4** | THF | 81 | 85 | 1 |
| 11 | **L4** | DME (1%$H_2O$) | NA | 20 | 3.7 |
| 12 | **L3** | DME (1%$H_2O$) | NA | 1.5 | 0 |

[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M for 4−24 h at 23 °C using 2.5 mol % **2** and 5.5 mol % ligand. [b] The ee values (in percent) were determined by chiral GC. [c] The yields (in percent) were determined by quantitative GC analysis using decane as internal reference.

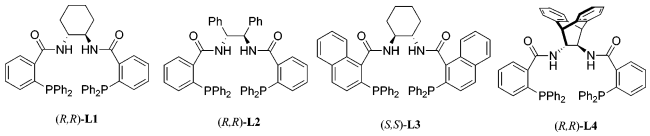



***Figure 1.*** Chiral ligands used in optimization studies.

With success in the creation of quaternary carbon centers, attention turned to creation of tertiary centers without product racemization. Optimization studies were explored using the enol carbonate of 1-tetralone **5** as summarized in eq 3 and Table 3. In contrast to the quaternary cases, toluene was not the preferred solvent. While the ee was satisfactory, significant amounts of unalkylated **7** and dialkylated **8** ketones were detected. Somewhat surprisingly, while THF proved to be slightly worse, dioxane gave excellent results. A possible rationale for this effect may be due to the observation that dioxane is better than THF in forming solvent-caged contact ion pairs.[11] Thus, if the alkylation reaction between the contact ion pairs is much faster than the diffusion rate of the ions or the product out of solvent cages, equilibrium of the initial enolate and the product will be minimized; as a result, higher yield of the monoalkylated product and better enantioselectivity will be



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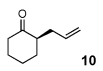
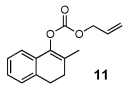
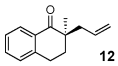
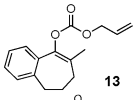
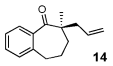
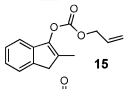
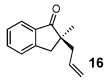
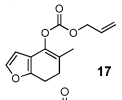
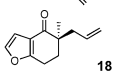
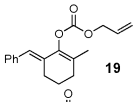
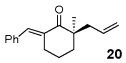
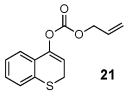
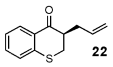
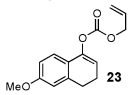
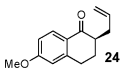
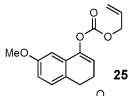
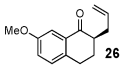
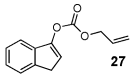
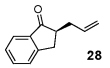
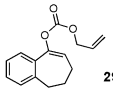
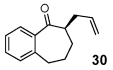
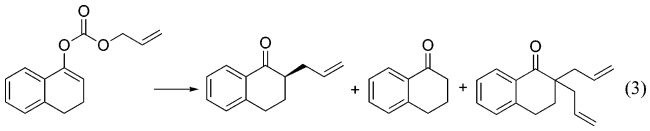
***Table 2.*** Reaction of Various Allyl Enol Carbonates[a]

| entry | substrate | product | yield[b] | ee[c] |
|---|---|---|---|---|
| 1[d] |  9 |  10 | 78% | 78%[e] |
| 2[d] |  11 |  12 | 88% | >99% |
| 3 |  13 |  14 | 94% | 91%[e] |
| 4[b] |  15 |  16 | 98% | 76% |
| 5 |  17 |  18 | 64% | 82% |
| 6 |  19 |  20 | 99% | 95% |
| 7 |  21 |  22 | 89% | 93% |
| 8[f] |  23 |  24 | 90% | >99% |
| 9[f] |  25 |  26 | 97% | 97% |
| 10 |  27 |  28 | 87% | 81% |
| 11[f] |  29 |  30 | 93% | 99% |

[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M in toluene at 23 °C for 20 h using 2.5% **2** and 5.5% ligand **L4**. [b] The yields were isolated yields. [c] The ee values were determined by chiral HPLC. [d] The $[\alpha]_D$ of the product has the same sign as that reported for the *R* configuration.[4,12] [e] The ee was determined by chiral GC. [f] Dioxane was used as solvent for the reaction.

***Table 3.*** Selected Optimization Studies for Alkylation at Secondary Carbon[a]

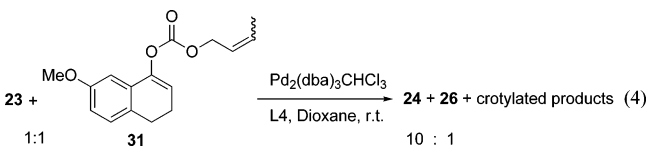



(3)

| entry | *T* (°C) | solvent | ee[b] | yield of **6**[d,e] | yield of **7**[e] | yield of **8**[e] |
|---|---|---|---|---|---|---|
| 1 | 23 | toluene | 95 | 62[c] | 29[c] | |
| 2 | 4 | toluene | 95 | 53(52)[c] | 36(39)[c] | 8 |
| 3 | 23 | THF | 94 | 51(51)[c] | 25(35)[c] | 5 |
| 4[b] | 23 | THF | 94 | 48(48)[c] | 25(32)[c] | 9 |
| 5 | 50 | THF | 89 | 46(44)[c] | 13(20)[c] | 19 |
| 6[b] | 50 | THF | 89 | 22(18)[c] | 7(10)[c] | 38 |
| 7 | 23 | dioxane | 97 | 81(81)[c] | 6 | <2 |

[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M for 20 h at 23 °C using 2.5% **2** and 5.5% ligand **L4**; yields were measured by quantitative GC analysis using decane as internal reference. [b] The ee values (in percent) were determined by chiral HPLC. [c] The yields were for isolated compound. [d] The $[\alpha]_D$ of **6** has the same sign as that reported for the *R* configuration.[2a] [e] Values are in percent.

obtained. To probe our proposal, we conducted a crossover experiment (eq 4), in which the 1:1 mixture of enol carbonate **23** and **31** was subjected to the Pd catalyst in dioxane. GC analysis of the product mixture revealed a 10:1 mixture of **24** and **26** in addition to crotylated products, indicating only minor leakage from the caged contact ion pairs in dioxane.




This alkylation was examined in a range of five-, six-, and seven-membered ketones (Table 2, entries 1, 7−11). In all cases, good to excellent yields of monoalkylated products were obtained. The simplicity of the cyclohexanone substrate makes it the most challenging, yet a respectable 78% ee was observed (Table 2, entry 1). Annealing an aromatic ring enhanced the ee to >90% (Table 2, entries 8 and 9). Using a heterocycle had no effect (Table 2, entry 7). While the ee dropped somewhat in the case of indanone (Table 2, entry 10), it increased to near perfect in the case of the benzosuberone (Table 2, entry 11).

In summary, an excellent method for the asymmetric allylation of simple ketones to create both quaternary and teriaycenters using the Pd AAA has been developed. The success of the method stems from the neutrality of the conditions and the tethering of the allylating agent to the nucleophile by a $CO_2$ unit. The excellent results obtained in both series combined with the change in facial selectivity compared to the use of lithium enolates in cases where that approach is applicable raises questions as to the exact mechanism of this reaction. Studies to elucidate the mechanism are necessary to understand the source of the enantioselectivity, and they are underway.

**Acknowledgment.** We thank the National Science Foundation and National Institutes of Health, GM13598, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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