Asymmetric Alkylation of β-Ketoesters

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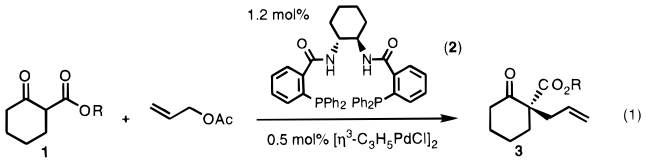
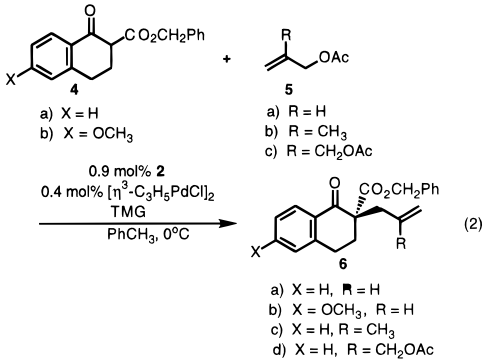
Creating quaternary carbon centers in which the absolute stereochemistry can be controlled by alkylation represents a major challenge. β-Ketoesters become interesting substrates because the structural diversity of the substituents permits ready and selective manipulation. Conceptually, catalytic asymmetric alkylations of such substrates are not straightforward.[1] Extrapolation of the concept of asymmetric allylic alkylations[2] to induce absolute stereochemistry in a prochiral nucleophile is tenuous, at best, given the known stereochemistry of the process.[3] As depicted in Figure 1, the pronucleophile resides very distal to the chiral ligands in the transition state for alkylation. Not surprisingly, the best ee's for alkylation of 2-carboethoxycyclohexanone have been less than 30%[4] although with a β-diketone significantly higher ee's have been obtained.[4−7] An imaginative solution to this problem arises in the case of α-cyanoesters wherein a chiral rhodium complex activates the pronucleophile—thereby bringing the asymmetric inducing ligands more proximal to the nucleophilic center.[8] An alternative strategy examines whether the geometric requirements of a chiral pocket would permit its chirality to be transmitted to the pronucleophile as depicted in Figure 1. We wish to report the feasibility of this strategy for the alkylation of β-ketoesters and the application of this methodology to a simple synthesis of the spiro-alkaloid nitramine.[9]

The reaction of 2-carboalkoxycyclohexanone (**1**) with allyl acetate using the chiral ligand (**2**) in a Pd catalyzed reaction was examined as summarized in eq 1 and Table 1. The results of Table 1 reveal the sensitivity of the reaction to conditions. Choice of base and solvent have dramatic effects. Both parameters would be expected to influence the exact structure of the nucleophile both in terms of the nature of the ion pair and the state of aggregation. The use of a highly delocalized cation, *N*,*N*,*N*′,*N*′-tetramethylguanidinium (TMG), in a nonpolar solvent, toluene (entry 6), proved most expeditious. The choice



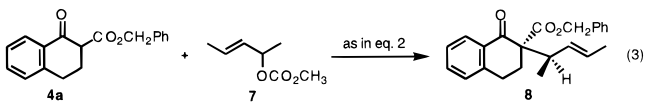
of ester, ethyl vs methyl vs benzyl, had no effect with sodium carbonate in methylene chloride (entry 4 vs 7 vs 9) and a small but notable effect with TMG in toluene (entry 6 vs 8 vs 10). Preparatively, performing the reaction at 1 M concentration of **1** (R = C_2H_5) for 24 h at room temperature with **2** as ligand gave a quantitative yield of *S*-**3** of 86% ee. Expectedly, using the *S*,*S* ligand corresponding to **2** gave *R*-**3** quantitatively also of 86% ee. Thus, both enantiomers of **3** are equally available. The absolute configuration was assigned by comparison to the literature.[4,10]

The tetralone system showed somewhat higher selectivities as shown in eqs 2−4 and Table 2. An initial experiment with the methyl ester corresponding to **4a** with allyl acetate gave the allylated product in 97% yield of 77% ee, whereas the benzyl ester gave the product **6a**[11] of 89% ee (eq 2 and Table 2, entry 1). As a result, the benzyl ester was employed for the



subsequent studies. In general, the reactions appeared to proceed more rapidly (cf. Table 1, entry 10 and Table 2, entry 1) than the simple cyclohexanone derivative. 6-Methoxytetralone gave a slight enhancement (Table 2, entry 2). Substituting the allylating agent showed the biggest effect (Table 2, entries 3−7). Using 2-substituted allylating agents gave excellent ee's, Table 2, entries 3 and 4.

With 1,3-disubstituted allylating agents, the issue of diastereo- as well as enantioselectivity arises. 3-(Methoxycarboxy)-2-pentene (**7**) gave excellent diastereoselectivity and enantioselectivity (Table 2, entry 5). Typically, this substrate does not participate well with almost all chiral ligands for asymmetric induction.[2] This observation demonstrates that with our ligands, excellent selectivity can be observed not only with respect to the allyl system[12] but also with respect to the nucleophile.



The effect of the geometry of the π-allylpalladium intermediate was explored. The acyclic example above involves a *syn*,*syn*-π-allylpalladium intermediate. Utilizing a cyclic substrate invokes the intermediacy of an *anti*,*anti* complex. Such

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Table 1. Asymmetric Alkylation of 2-Carboalkoxycyclohexanone

entry	R	solvent	base	temp (°C)	time (h)	% yield[a]	% ee (er *S:R*)[b,c]
1	C_2H_5	THF	NaH	−78 to 20	16	88	−16 (42:58)
2	C_2H_5	$PhCH_3$	NaH	0 to 20	16	(60)	−21 (39.5:60.5)
3	C_2H_5	$PhCH_3$	*n*-C_4H_9Li	−78 to 20	16	(90)	−22 (39:61)
4	C_2H_5	CH_2Cl_2	Na_2CO_3	40	24	74	70 (85:15)
5	C_2H_5	CH_2Cl_2	TMG[d]	20	16	85	75 (87.5:12.5)
6	C_2H_5	$PhCH_3$	TMG[d]	20	16	86	86 (93:7)
7	CH_3	CH_2Cl_2	Na_2CO_3	40	16	61	71 (85.5:14.5)
8	CH_3	$PhCH_3$	TMG[d]	0	2	85	79 (89.5:10.5)
9	CH_2Ph	CH_2Cl_2	Na_2CO_3	40	12	24	72 (86:14)
10	CH_2Ph	$PhCH_3$	TMG[d]	0	3	81	86 (93:7)

[a] Isolated yields except those listed in parenthesis represent GC yields. [b] The ee was determined by HPLC using Chiralpak AD column. [c] Negative ee's reflect the fact that the major enantiomer obtained was opposite to that depicted in eq 1. [d] TMG = *N,N,N′,N′*-tetramethylguanidine.

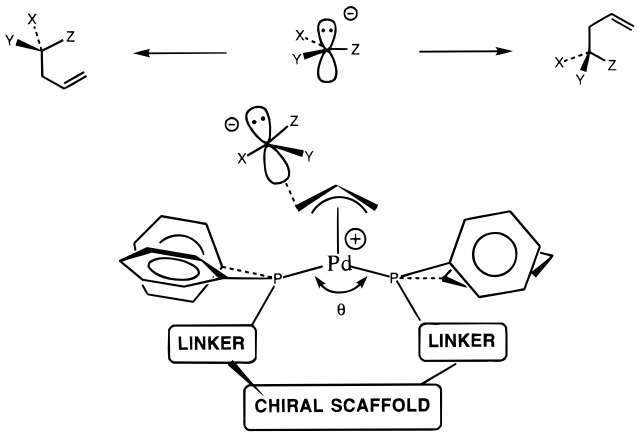


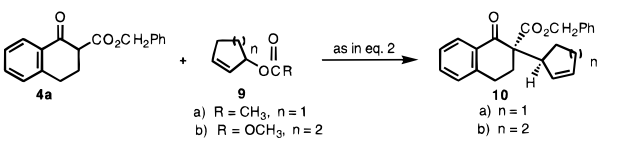
Figure 1. Geometrical issues for asymmetric induction at a pronucleophile in Pd catalyzed allylic alkylation.

Table 2. Enantioselectivity of Allylic Alkylation of Tetralones[a]

entry	tetralone	allylic ester	time	product % yield	dr	ee (er)[b]
1	**4a**	**5a**	0.25	**6a**, 94%		89 (94.5: 5.5)
2	**4b**	**5a**	1	**6b**, 98%		91 (95.5:4.5)
3	**4a**	**5b**	3	**6c**, 81%		95 (97.5:2.5)
4	**4a**	**5c**	1.5	**6d**, 80%		94 (97:3)
5	**4a**	**7**	3	**8**, 71%	94:6	97[c] (98:2)
6	**4a**	**9a**	2	**10a**, 87%	99:1	96[c] (98:2)
7	**4a**	**9b**	3	**10b**, 91%	98:2	99[c] (99.5:0.5)

[a] All reactions were run with 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, 0.9 mol % **2**, 1.2−1.4 equiv of TMG, 1.2−1.7 equiv of allyl ester, in toluene (0.2−0.4 M in tetralone) at 0 °C. [b] Enantioselectivities determined by HPLC using a Chiracel OD column eluting with heptane−isopropyl alcohol mixtures. [c] Enantioselectivity of major diastereomer.

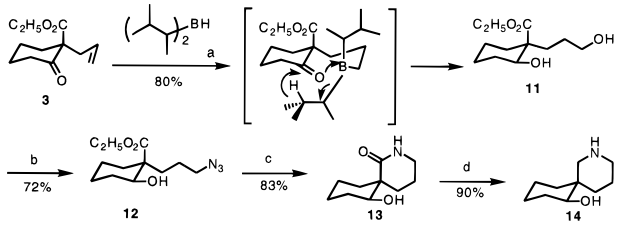
substrates have given excellent enantioselectivities with achiral nucleophiles.[13] As illustrated in eq 4 and Table 2, entries 6 and 7, these cyclic allylic esters gave even higher diastereoselectivities and excellent enantioselectivities. The stereochemistry is assigned only by analogy to our previous observations. In the cases of **6a**−**d**,[11] the assignments are by analogy to the absolute configuration established for **3**. In the cases of **8**,[11] **10a**,[11] and **10b**,[11] the assignments are by analogy to the established sense of asymmetric induction with respect to the allyl systems as well as for **3**.[12,13]



(4)

The ability to effect asymmetric induction in the alkylations of β-ketoesters can be quite useful. As an example, we undertook a simple synthesis of the spiro-alkaloid nitramine (**14**),[14] representative of a class of such alkaloids that have shown interesting biological activities.[15] Scheme 1 outlines the synthesis from **3**. Hydroboration of the alkene with disiamylborane followed by oxidative workup with sodium perborate[16] gave a single diol **11**. Thus, a novel diastereoselective ketone reduction accompanied alkene hydration presumably by a mechanism depicted in Scheme 1.[17] Activation of the primary alcohol as the mesylate allowed chemoselective substitution with azide to give hydroxyazide **12**. Catalytic reduction at room temperature produced the amino group which required heating at reflux to effect complete cyclization to lactam **13**[14b,g,h] whose recrystallization from ethyl acetate enhanced the ee to 95%. Reduction of the latter gave (−)-nitramine, identical in properties to those previously reported.[9,14] From 2-carboethoxycyclohexanone, this alkaloid is synthesized asymmetrically in six steps and 43% overall yield.

Scheme 1. An Asymmetric Synthesis of (−)-Nitramine (**14**)[a]



[a] (a) THF, −15 °C to room temperature then $NaBO_3.4H_2O$, H_2O. (b) i. $(C_2H_5)_3N$, CH_3SO_2Cl, −60 °C → 0 °C, CH_2Cl_2; ii. NaN_3, DMF, 40 °C. (c) H_2 (1 atm), $Pd(OH)_2$/C, K_2CO_3, C_2H_5OH, room temperature to reflux. (d) LAH, THF; room temperature.

This report represents the first examples of catalytic asymmetric alkylation of β-ketoesters with high ee's. The presence of three different functional groups (ketone, ester, and allyl) on the stereogenic center provide great flexibility for further structural elaboration. It appears that this family of ligands may be tailored for the asymmetric alkylation of pronucleophiles. However, since so many variables exist for each different nucleophile, fine tuning for each would appear likely to be needed. For example, alkylation of 2-benzyloxycarbonylindanone, under the general conditions for the cyclohexanone derivatives, gave the desired product in 99% yield with 65% ee. These promising results suggest that such asymmetric alkylation of prochiral β-ketoesters may become reasonably general.

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Supporting Information Available: Characterization data for **3**, **6a**−**d**, **8m**, **10a,b**, and **11**−**14** illustrative experimental procedure, and table of enantioselectivity assay data (5 pages). See any current masthead page for ordering and Internet access instructions.

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