Atom Economic Asymmetric Creation of Quaternary Carbon: Regio- and Enantioselective Reactions of a Vinylepoxide with a Carbon Nucleophile

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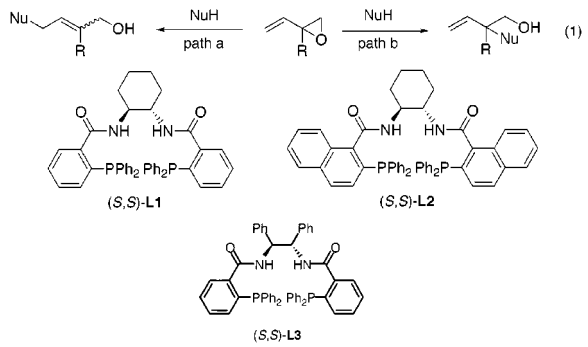
The metal-catalyzed additions of pronucleophiles to vinylepoxides with achiral phosphine ligands have a strong bias to lead to 1,4-addition (eq 1, path a), due to the electronic effect of the epoxide oxygen.[1,2] On the other hand, the 1,2-adducts are



potentially valuable chiral building blocks as a result of the diverse functionality present that permits chemoselective differentiation. While the use of heteroatom pronucleophiles such as alcohols, amines, and imides has been successfully employed,[3−5] the use of carbon-centered pronucleophiles has not been employed yet represents perhaps the most significant type since it builds the basic carbon framework. Particularly significant is the case of R = alkyl since it entails creating a quaternary carbon enantioselectively. The success of heteroatom pronucleophiles has been attributed to the ability of such functionality to hydrogen bond or in some other way coordinate to the epoxide oxygen to help deliver the nucleophile to the adjacent carbon. The failure of carbon-centered pronucleophiles to participate in such hydrogen bonding would seem to make any extrapolation of results from heteroatom to carbon pronucleophiles unlikely. Despite this expectation, we explored β-ketoesters in such reactions to determine the feasibility of eq 1, path b, dominating over path a.

As a probe of the effect of chiral ligands on regioselectivity, isoprene monoepoxide **1** was reacted with ethyl acetoacetate **2** in the presence of 1 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd(0)) and 3 mol % of racemic ligand **(±)-L1** (eq 2, and Table 1, entry 1). A

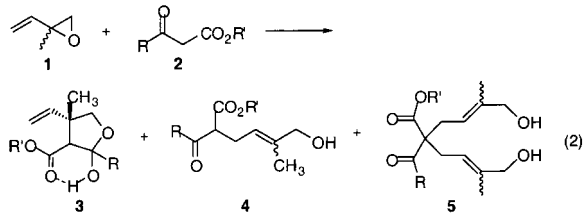


Table 1. Probe Reactions of 2-Methyl-2-vinyloxirane with Ethyl Acetoacetate[a]

entry	ligand	additive[b]	solvent	temp	rxn time (min)	ratio[c] **3:4:5**	yield[d] **3**	ee[e] **3**
1	(±)-**L1**	none	CH_2Cl_2	rt	10	79:16:5	64	n.a.[f]
2	(±)-**L1**	none	CH_2Cl_2	0 °C	30	54:22:24	n.d.[g]	n.a.[f]
3	(*S,S*)-**L1**	none	CH_2Cl_2	rt	25	63:24:14	45	93
4	(*S,S*)-**L1**	TBAT	PhH	rt	15	73:16:11	56	93
5	(*S,S*)-**L2**	none	CH_2Cl_2	rt	30	60:30:10	48	96
6	(*S,S*)-**L2**	TBAT	PhH	rt	<5	70:17:13	57	97
7	(*S,S*)-**L3**	TBAT	PhH	40 °C	70	79:17:4	70	96
8[h]	(*S,S*)-**L3**	TBAT	PhH	40 °C	120	n.d.[g]	68	94

[a] All reactions were conducted on 0.5 mmol scale in 5.0 mL of solvent using 1.0 equiv of **1**, 1.1 equiv of **2**, 1 mol % of $Pd_2dba_3{\cdot}CHCl_3$, and 3 mol % of ligand unless indicated otherwise. [b] When added, 1 mol % employed. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Isolated yield of pure **3**. [e] Determined after dehydration of initial adduct. [f] n.a. = not applicable. [g] n.d. = not determined. [h] Rection performed with 0.5 mol % of catalyst used at 0.2 M concentration.

mixture of the 1,2 (i.e., **3**)- and 1,4 (i.e., **4** and **5**)-adducts were obtained from which the 1,2-adduct **3a**[6] was isolated pure in 64% yield. Lowering the temperature decreased the selectivity (entry 2). Interestingly, using enantiopure ligand ***S,S*-L1**[7] also reduced the selectivity (entry 3), which allowed isolation of pure **3** in only 45% yield. Gratifyingly, the enantioselectivity was excellent (93% ee, determined after conversion to the corresponding dihydrofuran **6**). The reduced regioselectivity with the enantiopure ligand compared to that of the racemic ligand was attributed to a kinetic discrimination in the initial ionization with racemic epoxide and racemic ligand to favor formation of enantiomers of the same diastereomer **I-1** (Figure 1) of the intermediate π-allylpalladium species which had an intrinsic higher preference for addition at the more substituted allyl terminus. With the enantiopure ligand and racemic epoxide, two different diastereomeric π-allylpalladium intermediates **I-1** and **I-2** are formed. While **I-1** favors formation of the branched product, its diastereomer **I-2** favors formation of the linear product.

It was hypothesized that increasing the rate of interconversion of diastereomeric π-allylpalladium complexes would increase the regioselectivity and maintain the ee.[8] Indeed, adding 1 mol % TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate) did just that (entry 4). A similar trend was observed with the more sterically congested ligand **L2**[4c] (entries 5 and 6). The more flexible ligand **L3**[7] gave the best results, wherein a 70% isolated yield of **3** of 96% ee was obtained (entry 7). Reducing the catalyst load and increasing the concentration, each by a factor of 2, showed little change (entry 8).

A range of β-ketoesters were examined as summarized in Table 2. Varying the size of the ester group R′ had little effect on the selectivity. On the other hand, increasing the size of R does increase the regioselectivity. In all cases, the enantioselectivity

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Table 2. Examples[a]

	2				Ratio[c]	Yield[d]	ee[e]
Entry	R	R'	Method[b]	Time(h)	**3 : 4 : 5**	**3**	**3**
1	CH_3	C_2H_5	a[f]	1.2	79:17:4	70 (**3a**)	96
2	CH_3	n-C_4H_9	a[f]	1	82:14:4	65 (**3b**)	97
3	CH_3	t-C_4H_9	a[g]	24	77:17:6	65 (**3c**)	95
4	CH_3	$PhCH_2$	a[g]	2.5	72:19:9	61 (**3d**)	95
5	C_2H_5	C_2H_5	a[f]	4	80:17:3[i]	71 (**3e**)	96.5
6	CH_2=$CH(CH_2)_8$	C_2H_5	b[h]	2.5	80:13:7[i]	71 (**3f**)	95
7	$PhCH_2$	C_2H_5	a[h]	2	n.d.	71 (**3g**)	93.5
8		C_2H_5	b[g]	2.5	80:13:7[i]	70 (**3h**)	98
9	i-C_3H_7	C_2H_5	b[g]	2.3	81:17:2[i]	74 (**3i**)	97
10		C_2H_5	b[g]	11	90:10:-	74 (**3j**)	99
11		C_2H_5	b[g]	11	90:10:-	80 (**3k**)	97
12	Ph	C_2H_5	a[f]	1.25	77:23[i]	59 (**7c**)[j]	98.5[k]
13	p-O_2N-C_6H_4	C_2H_5	b[h]	< 5 min	n.d.	57 (**3m**)	95[k]

[a] All reactions conducted on 0.5 mmol scale in 5 mL of solvent using 1 mol % Pd_2dba_3·$CHCl_3$ and 3 mol % ligand. [b] Method a: (*S,S*)-**L3** and 1 mol % TBAT in PhH at 40 °C. Method b: (*S,S*)-**L1** in CH_2Cl_2 at rt (no additive). [c] Determined by ^{1}H NMR on crude mixture unless indicated otherwise. [d] Isolated yield of pure **3**; also see ref 6. [e] Determined after dehydration of initial adduct. [f] Ratio of **1**: **2** = 1:1.1. [g] Ratio of **1**: **2** = 1.3:1. [h] Ratio of **1**: **2** = 1.2:1. [i] Ratio of isolated products. [j] See text. [k] Determined after conversion to **7c** or **7d**.

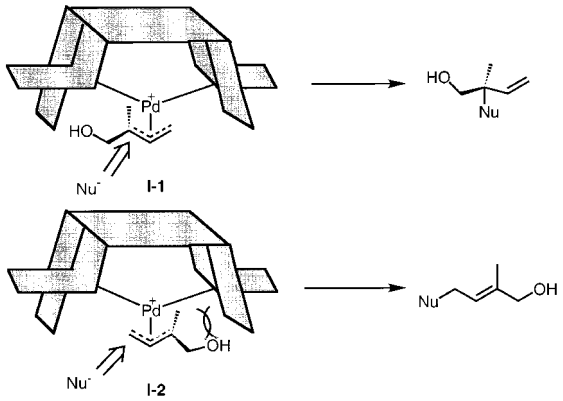
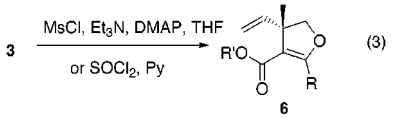
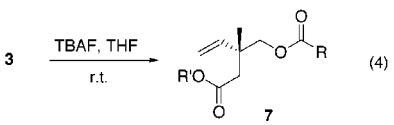


Figure 1. Cartoon rationalizing regioselectivity.

is excellent—ranging from 93.5 to 99%. Because the hemiacetals **3** were mixtures of diastereomers, they were dehydrated to form the dihydrofurans **6**,[6] typically in 60−87% yields (eq 3). Chiral



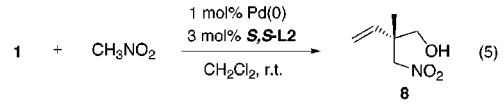
HPLC analysis on a Chiralcel OD column or GC analysis on a cyclosil B column of the resultant dihydrofurans allowed determination of ee as well as demonstrated a synthetic application. Interestingly, acyl transfer of the β-ketoester products occurred upon treatment of **3** with TBAF (eq 4). In the case of ethyl benzoyl



a: R = CH_3, R' = C_2H_5 73%
b: R = i-C_3H_7, R' = C_2H_5 97%
c: R = Ph, R' = C_2H_5 see text
d: R = 4-$O_2NC_6H_4$, R' = C_2H_5 100%

acetate, the adduct **3l** spontaneously formed **7c** when the alkylation was performed in the presence of TBAT. Thus, the product of entry 12 was directly **7c**[6] although **3l** could be isolated if no TBAT was employed. Thus, this reaction serves as a convenient method to effect an asymmetric alkylation with the enolate of acetate and provide simultaneous protection of the primary alcohol. The resultant product **7** also provided access to *S*-3-methyl-3-vinyl-D-butyrolactone upon treatment with 1.2 equiv of methanolic sodium hydroxide in 70% yield. Hydrogenation over Adam's catalyst at 1 atm of hydrogen in methanol gave *S*-3-ethyl-3-methyl-D-butyrolactone, $[\alpha]_D$ +15.6 (*c* 3.33, $CHCl_3$), establishing the absolute configuration.[9]

Since achiral ligands give 1,4-adducts, these reactions demonstrate the unique property of the chiral ligands to control regio- as well as enantioselectivity. The results reported herein represent the first examples of such control of regioselectivity for carbon-centered nucleophiles reacting with vinyl epoxides.[10] Good yields of the desired 1,2-adducts can be obtained with a diverse array of β-ketoesters. Such carbon nucleophiles appear not to be unique. For example. nitromethane provided the corresponding adduct **8**[6] in 51% yield and 97% ee (eq 5). The source of this effect can



be understood on the basis of the current model used to rationalize the reactions with this family of ligands and thus provides additional support for this model. These reactions represent simple additions with anything else being employed catalytically and thus are atom economic.[11] They create a chiral quaternary center with three of the groups being quite different functional groups and thus allow easy manipulation of any one in the presence of the others. As such, they should be useful building blocks.

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Supporting Information Available: Complete experimental procedures for catalytic addition, dehydration, and acyl migration and characterization data for **3a**−**m, 6a**−**k**, **7a**−**d**, and **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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