Ester Enolate Alkylations

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Palladium-Catalyzed Allylic Alkylation of Carboxylic Acid Derivatives: *N*-Acyloxazolinones as Ester Enolate Equivalents**

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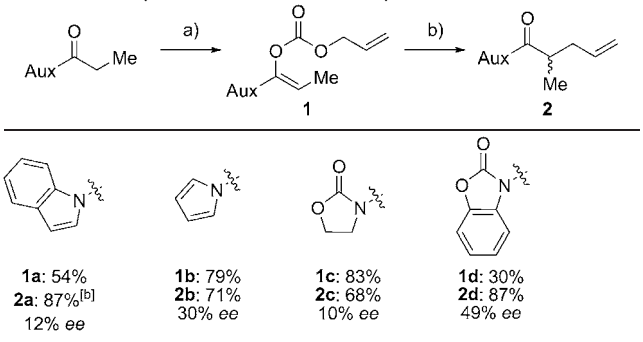
The asymmetric alkylation of carbonyl compounds is one of the most important methods for generating stereocenters in organic synthesis.[1] The alkylation of ester enolates is particularly useful as the resulting products can be converted into a variety of carboxylic acid derivatives or reduced to alcohols without loss of enantioenrichment at the α center.[2] The most common procedures for asymmetric ester enolate alkylations, however, involve the use of stoichiometric chiral auxiliaries.[3,4] Attempts to render this asymmetric transformation catalytic have achieved only limited success. For example, successful asymmetric alkylations of specialized carboxylic acid derivatives including oxindoles,[5] azalactones,[6] and zinc enolates of glycine esters[7] have been reported. A recent example of an asymmetric Pd-catalyzed Claisen rearrangement of allyl phenylacetate demonstrated an alternative strategy for obtaining enantioenriched ester derivatives.[8] While these reports demonstrate the continued importance of developing asymmetric alkylations of ester derivatives, a highly general and enantioselective alkylation of simple ester derivatives is still elusive.[9]

As a solution to this unmet need, we and others have recently reported the use of ester enolate surrogates in the asymmetric allylic alkylation (AAA) reaction, including 2-acylimidazoles,[10] *N*,*N*-dialkyl amides,[11] and acylsilanes.[12] However, there are several drawbacks to each of these methods. First, the acylimidazoles and acylsilanes require multiple steps to synthesize from carboxylic acids. Second, subsequent transformations that take advantage of the reactivity of the carboxylic acid functionality are not straightforward. Thus, a general enantioselective method for enolate alkylations of simple ester derivatives that can function directly in subsequent transformations is still elusive.[13] We report herein the palladium-catalyzed asymmetric alkylation of *N*-acylbenzoxazolinone-derived enol carbonates, which represents a general asymmetric alkylation of ester enolate equivalents at the carboxylic acid oxidation state.[14] Importantly, the resulting enantioenriched imide products are easily converted into the acid, ester, thioester, amide, or alcohol derivatives under mild conditions without prior activation. In addition, the modularity of our diamino bis(phosphine) ligands allowed for a new strategy for catalyst design wherein the steric properties of the diaryl phosphines was varied to enable high enantioselectivity.

From the outset, our goal was to develop an enantioselective ester enolate alkylation where the products could be easily derivatized under mild conditions to a variety of carboxylic acid derivatives. Thus, our initial studies focused on employing ester surrogates at the carboxylic acid oxidation state that are known to hydrolyze under mild conditions (Table 1). One significant advantage of using these activated

Table 1: Auxiliary screen of ester enolate equivalents.[a]



[a] Reactions performed on 1–2 mmol scale. Yields are of the isolated products. Enantiomeric excess (*ee*) values determined by HPLC analysis on a chiral stationary phase; absolute configuration of **2a**–**c** not determined. Reagents and conditions: a) NaHMDS, DME, −78 °C, then allylchloroformate; b) $[Pd_2dba_3]\cdot CHCl_3$ (2.5 mol %), **4** (6 mol %), dioxane, RT, 16 h. DME = 1,2-dimethoxyethane, dba = dibenzylideneacetone, NaHMDS = sodium bis(trimethylsilyl)amide. [b] Run in toluene.

esters over previously reported systems is the ability to quickly access substrates in one step from any carboxylic acid by amide bond formation. A major challenge in the alkylation of ester derivatives is the propensity of the intermediate enolate to undergo elimination to form a ketene. We believed that the recently developed decarboxylative allylic alkylation methodology[15,16] provided a unique way to avoid this problem because the enolate could be trapped as an enol carbonate at low temperature where competing ketene formation would be minimized. The enol carbonate might then be purified and employed in the AAA reaction. In our initial studies, we found that a variety of enol carbonates derived from ester equivalents could indeed be isolated, including *N*-acyl imidazoles, indoles, and oxazolinones (Table 1). In the ensuing decarboxylative asymmetric alkylation reaction using our anthracenediamine-derived bisphosphine ligand **4** (see below), the best yield and enantioselec-

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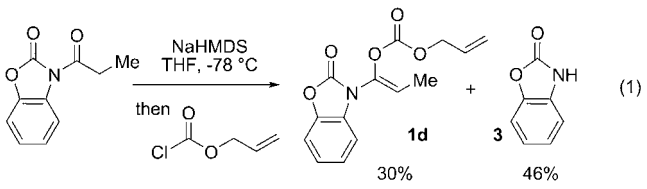
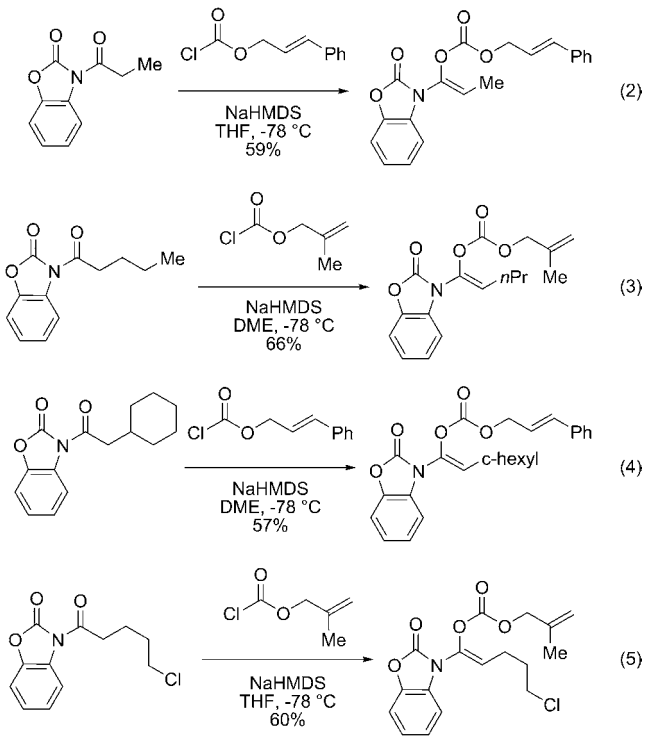
tivity was observed with *N*-acylbenzoxazolinone-derived substrate **1d**. Further optimization studies, therefore, focused on the *N*-acyloxazolinone-derived enol carbonates as substrates for the asymmetric alkylation reaction.

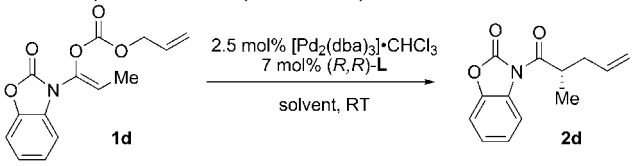
The major challenge with employing the benzoxazolinone-derived enol carbonates was the low yield of the enol-forming reaction. Careful analysis of the crude reaction mixture showed that the remainder of the yield was consumed by side reactions resulting from ketene elimination, with benzoxazolinone **3** as the major side product [Eq. (1); THF = tetrahydrofuran]. As a solution to this problem, we found that formation of the enolate in the presence of the chloroformate provided the desired product **1d** in much improved and synthetically useful yields (65%). Our optimization studies also demonstrated that the chloroformate acylating agent was necessary for efficient generation of the enol carbonate. This new procedure for enol carbonate formation proved exceptionally general. For instance, a wide range of chloroformate electrophiles could be employed in the process, including those substituted at the terminal [Eq. (2), (4)] and internal positions of the olefin [Eq. (3), (5)]. The tolerance for substitution on the *N*-acylbenzoxazolinone partner also proved to be very general. Enol carbonates bearing longer alkyl chains [Eq. (3)], β,β-disubstituted carbons [Eq. (4)] and a variety of functional groups including primary alkyl chlorides [Eq. (5)] could all be isolated in good yield. These enol carbonates are relatively stable and can be stored at low temperature for several months without decomposition.





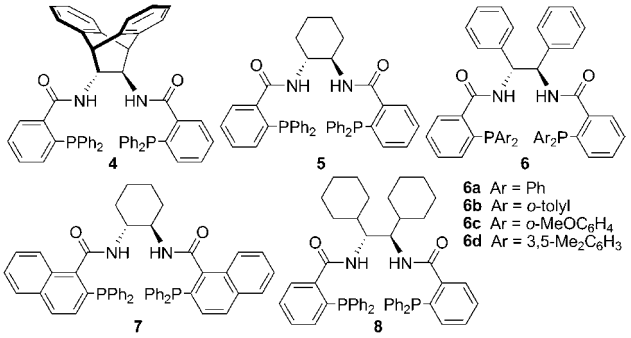
Having established that imide-derived enol carbonates could be synthesized in good yield, we then sought to improve the enantioselectivity of the asymmetric alkylation process (Table 2). By varying both the ligand (entries 1–4) and solvent (entries 5–8), we found that the product could be obtained with 75% *ee* using the stilbene diamine-derived bisphosphine ligand **6a** in THF as solvent. We next varied the structure of the phosphine ligand, believing that increasing the steric bulk around the phosphines could increase the selectivity of the reaction. We were pleased to find that this was indeed the case; *o*-tolyl-substituted bisphosphine **6b** gave the product in higher enantioselectivity (entry 9). This new approach to ligand modification further demonstrates the modularity of our class of enantiopure bisphosphine ligands and the ability to selectively tune both the steric and electronic properties of the ligand to improve selectivity. Other substitution on the phosphine, however, did not lead to an increase in selectivity

Table 2: Optimization of asymmetric alkylation reaction.



Entry[a]	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	**4**	dioxane	87	49
2	**5**	dioxane	88	62
3	**6a**	dioxane	96	64
4	**7**	dioxane	83	60
5	**6a**	toluene	99	75
6	**6a**	CH_2Cl_2	66	63
7	**6a**	THF	96	75
8	**6a**	DME	99	73
9	**6b**	**THF**	**99**	**85**
10[d]	**6c**	THF	12	54
11	**6d**	THF	25	30
12	**8**	THF	22	60

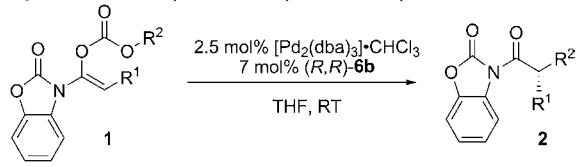
[a] Reactions run using 0.2 mmol enol carbonate **1d**, 0.005 mmol $[Pd_2(dba)_3]\cdot CHCl_3$, and 0.014 mmol ligand at 0.2 M for 10–30 min. [b] Yield of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Run for 12 h.

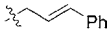
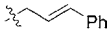
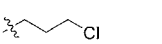
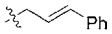
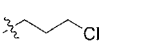
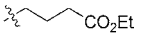
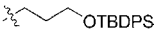
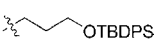


(entries 10, 11). In addition, varying the structure of the diamine backbone to the 1,2-dicyclohexylethane diamine (**8**) led to decreased yield and enantioselectivity (entry 12).

With optimal conditions in hand, we next explored the substrate scope of the asymmetric alkylation reaction (Table 3). In general, the substituted allyl carbonates proved

Table 3: Substrate scope for the asymmetric alkylation reaction.

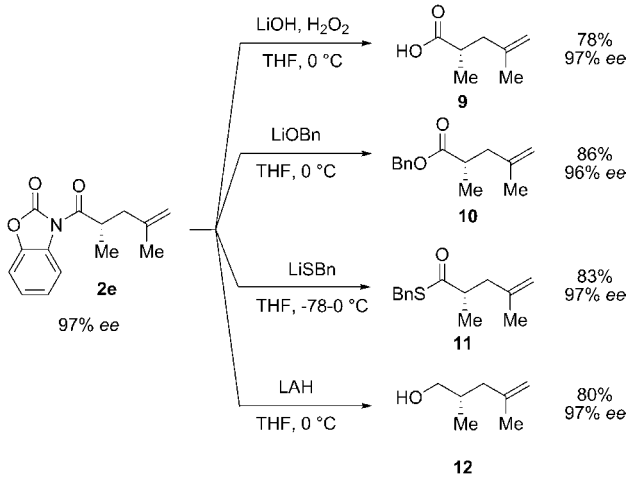


Entry[a]	R^1	R^2		Yield [%][b]	*ee* [%][c]
1	Me		**2d**	99	85
2	Me		**2e**	89	97
3[d]	Me		**2f**	82	82
4[e]	Me		**2g**	58	99
5[d,f]	Me		**2h**	96	90
6[g]	Et		**2i**	68	88
7[h]	Et		**2j**	93	97
8[h]	*n*Pr		**2k**	76	97
9[f]	*n*Pr		**2l**	83	92
10[h]			**2m**	94	95
11	CH_2Ph		**2n**	73	94
12	cyclohexyl		**2o**	77	80
13[f]	cyclohexyl		**2p**	80	83
14[h]			**2q**	66	95
15[g]			**2r**	71	79
16[h]			**2s**	94	95
17[d]			**2t**	72	81

[a] See Table 1 for experimental details. Reactions run on 0.1–0.2 mmol scale for 4–24 h. [b] Yield of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Using ligand **6a**. [e] Diastereomeric ratio of **2g** is >95:5, see Ref. [14] for relative stereochemistry assignment. [f] Linear/branched ratio of **2h**, **2l**, **2p** is >10:1. [g] Run at 50 °C. [h] Run with 5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 14 mol% **6b**.

to be excellent substrates. Specifically, substitution at the internal position of the olefin (entries 2, 3), the allylic position (entry 4) or the terminus of the olefin (entry 5) is tolerated and in most cases serves to increase the enantioselectivity of the reaction over the simple allyl electrophile. Where regioselectivity in the alkylation is possible, excellent regiomeric ratios are observed in favor of the linear product (entries 5, 9, 13, >10:1 linear/branched selectivity). In addition, the reaction proceeds with high diastereoselectivity when prochiral electrophiles are employed (entry 4, >95:5 d.r.).[17] The AAA reaction also proceeds efficiently with a variety of substituents at R^1. Mono- and disubstitution at the β position of the enol is tolerated (entries 6, 12). However, β,β-disubstituted enols (entries 12, 13) and longer alkyl chains (entry 15) gave a small decrease in the enantioselectivity of product formation. A variety of functional groups are also tolerated in the reaction, including primary alkyl chlorides (entry 14), esters (entry 15), and silyl ethers (entries 16, 17). This process is also readily conducted on large scale: when Table 3, entry 2 was conducted on 4.0 mmol scale, **2e** was obtained in 66% yield and 97% *ee*.

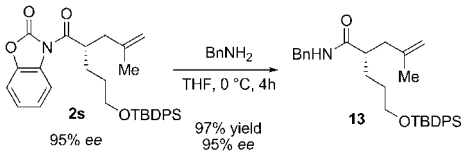
A major goal of this research was to develop an efficient asymmetric alkylation of ester enolate equivalents that could be derivatized to any number of carboxylic acid derivatives under mild conditions. We were delighted, therefore, to find that the alkylated products can be functionalized under very mild conditions without significant loss of enantiopurity (Scheme 1).[2] The benzoxazolinone moiety was cleaved



Scheme 1. Functionalization of chiral acylbenzoxazolidinone **2e**. Bn = benzyl, LAH = lithiumaluminum hydride.

efficiently to generate the corresponding acid (**9**), ester (**10**), and thioester (**11**) by simply treating the imide with the respective lithium anion of the nucleophile. In addition, reduction to the alcohol (**12**) proceeded in good yield. Importantly, little or no racemization of the α stereocenter of the products was observed for these transformations. The absolute stereochemistry of the alkylation was confirmed by comparison of acid **9** to previously reported materials.[18]

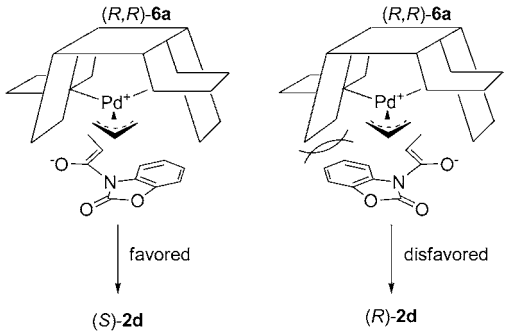
Having established that the benzoxazolinone auxiliary was an excellent leaving group for substitution reactions, we next wondered what additional nucleophiles could react with the enantioenriched imide products. We found that simple treatment of product **2s** with a primary amine led to formation of amide product **13** in just 4 h in high yield (97%) and with complete retention of enantiopurity [Eq. (6); TBDPS = *tert*-butyldiphenylsilyl]. This transformation demonstrates the mild reaction conditions under which substitution of the benzoxazolinone can occur, even when compared with Evans' chiral oxazolidinone auxiliary, which generally



(6)

requires stoichiometric trialkylaluminum additives to effect the analogous transformation.[19] In addition, this direct conversion into amide products is a marked improvement over our previous system[10] where the 2-acylimidazole products had to be converted into the carboxylic acid before subsequent amide bond formation, or racemization would occur.

The absolute sense of stereochemistry in this decarboxylative alkylation reaction can be rationalized using the wall and flap cartoon model,[20] which was developed in our laboratory to predict the selective formation of one enantiomer when the diphenylphosphinobenzoic acid-based chiral ligand scaffolds are employed. Using the *R*,*R* enantiomer of our stilbene diamine-derived ligand, our working model correctly indicates that selective formation of the *S* enantiomer of the allylation product should occur based on unfavourable steric interactions in the transition state for formation of the corresponding *R* enantiomer (Scheme 2). The selective formation of the *S* enantiomer in this reaction is also in accordance with the structure-based rationale presented by Lloyd-Jones and co-workers.[21]



Scheme 2. Transition-state model for enantioselectivity.

In summary, we report a general asymmetric allylic alkylation of ester enolate equivalents at the carboxylic acid oxidation state. Specifically, a variety of *N*-acylbenzoxazolidinone-derived enol carbonates can be generated in good yields and are excellent substrates for the palladium-catalyzed asymmetric alkylation reaction. For the first time, variation of the steric properties of the phosphine moiety on this class of bis(phosphine) ligands was shown to provide increased enantioselectivity in an allylic alkylation reaction. An important improvement over previous methods is that the activated ester derivatives are easily accessed from readily available carboxylic acids by simple amide bond formation. In addition, the enantioenriched imide products are readily transformed to the corresponding acid, ester, thioester, alcohol, and amide derivatives without need for prior activation or oxidation of the substrate, providing easy access to a variety of highly useful enantioenriched building blocks for organic synthesis.

Experimental Section

General procedure for synthesis of enol carbonates: Into a 25 mL round bottom flask was placed 3-propionylbenzo[d]oxazol-2(3*H*)-one (0.466 g, 2.43 mmol) and allylchloroformate (0.308 g, 2.56 mmol, 1.05 equiv) in 7 mL THF and the flask was cooled to −78 °C in a dry ice/acetone bath. To this solution was slowly added a −78 °C solution of sodium bis(trimethylsilyl)amide (0.492 g, 2.68 mmol, 1.1 equiv) in 7 mL THF via cannula. The reaction was stirred for 1 h then quenched with pH 7 phosphate buffer. The mixture was poured into a separatory funnel and the aqueous layer extracted with 3 × 30 mL Et_2O. The combined organics were dried over Na_2SO_4 and filtered through a short plug of silica gel. The solvent was then removed and the product purified on a column of silica gel, eluting with 5:1 hexanes/Et_2O to give 0.434 g (65 % yield) of the desired product **1d** as a colorless oil.

General procedure for asymmetric alkylation reaction: Into an oven-dried 2 Dram vial was placed $[Pd_2(dba)_3]\cdot CHCl_3$ (5.3 mg, 0.005 mmol, 0.025 equiv) and Trost stilbene ligand (*R*,*R*)-**6b** (9.5 mg, 0.012 mmol, 0.06 equiv), and the vial was flushed with argon from a balloon for 5 min. Freshly distilled and degassed THF (1 mL) was then added and the solution was sonicated at room temperature for ca. 20 min until the reaction turned from heterogeneous deep red to homogeneous deep red-orange in color. The catalyst solution was then transferred via syringe to a degassed 2 Dram vial containing **1d** (0.055 g, 0.2 mmol) in 1 mL degassed THF. The reaction was stirred 10 min, at which time TLC showed complete consumption of starting material. The solvent was then removed and the product was purified on silica gel with 8:1 then 6:1 hexanes/Et_2O as eluent to give 0.044 g (96 % yield) of the desired product with 85 % *ee*.

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