J|A|C|S COMMUNICATIONS

Published on Web 06/15/2010

Palladium-Catalyzed Asymmetric Allylic Alkylation of 2-Acylimidazoles as Ester Enolate Equivalents

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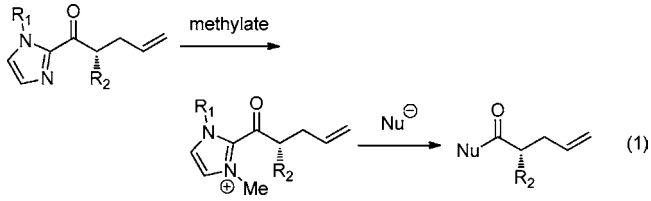
The stereocontrolled alkylation of carbonyl compounds is a staple reaction in organic synthesis for the construction of highly enantioenriched materials. In particular, the alkylation of ester enolate equivalents has found widespread use due to the versatility of the resulting ester or amide products.[1] Success in the field of ester enolate alkylations has relied on the use of chiral auxiliaries to direct the stereochemical outcome of the alkylation.[2] Catalytic asymmetric ester enolate alkylations, although more desirable, are rare.[3,4] Andrus and co-workers have reported the alkylation of a single 2-acylimidazole derivative (1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)ethanone)[5] with allylic and benzylic bromides that gives products with 75−99% ee under phase transfer catalysis using chiral cinchonidinium catalysts. They later disclosed a similar, albeit less stereoselective, alkylation of specifically phenethyl 2-naphthylacetate.[6] While promising, these examples have only been demonstrated for a 2-naphthyl substituent and require superstoichiometric amounts of base and alkylating agents. In this report we describe the first catalytic asymmetric allylic alkylation (AAA) of a broad range of 2-acylimidazole-derived enol carbonates, the products of which are easily converted to a variety of ketone and carboxylic acid derivatives.

The transformation of 2-acylimidazoles to carboxylic acid derivatives was first reported by Ohta and co-workers.[7] They found that while 2-acylimidazoles did not undergo acyl transfer reactions, alkylation of the imidazole nitrogen generated an activated leaving group that allowed substitution to occur (eq 1). Based on this finding, we envisioned expanding the scope of our AAA reaction of enol carbonates to include 2-acylimidazoles as the first efficient and general example of catalytic asymmetric alkylations of ester enolate equivalents.

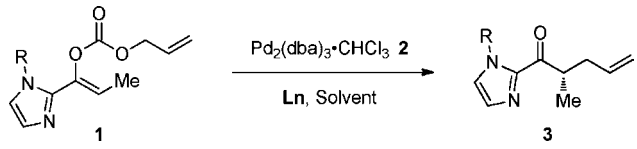


(1)

Our initial studies focused on the decarboxylative allylic alkylation reaction of allyl enol carbonates **1** catalyzed by $Pd_2(dba)_3 \cdot CHCl_3$ (**2**) and **L1** (Table 1, entries 1−4). While the reaction proceeded in a number of solvents, conducting it in dioxane generated alkylated product **3a** with the highest yield and ee (entry 1). Varying the N-substituent on the imidazole portion of the enol carbonate from methyl (**1a**) to phenyl (**1b**) led to higher yields and a higher ee of the product **3b** (entry 5). Further varying R to 2-methylphenyl (**1c**) or 1-naphthyl (**1d**) gave similar yields but led to a small decrease in the ee of the products **3c**−**d** (entries 6−7). In addition, varying the ligand from **L1** to **L2**−**L4** gave product **3b** in good yields, but with lower enantioselectivity.

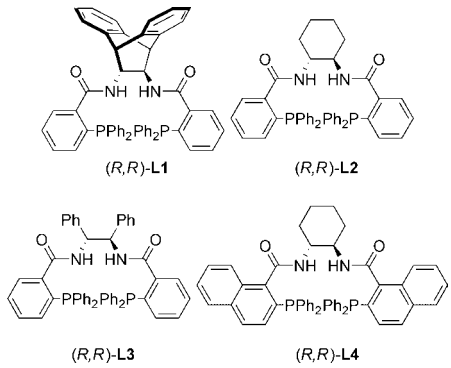
The reaction scope under our optimized conditions (Table 1, entry 5) is summarized in Table 2. A variety of acyclic and cyclic allylic

Table 1. Selected Optimization Studies



entry[a]	solvent	Nu	R	Ln	3	Yield (%)[b]	ee (%)[c]
1	Dioxane	**1a**	Me	**L1**	**3a**	89	87
2	CH_2Cl_2	**1a**	Me	**L1**	**3a**	10	n.d.
3	Toluene	**1a**	Me	**L1**	**3a**	83	76
4	THF	**1a**	Me	**L1**	**3a**	65	80
5	**Dioxane**	**1b**	**Ph**	**L1**	**3b**	**96**	**92**
6	Dioxane	**1c**	2-Tol	**L1**	**3c**	95	89
7	Dioxane	**1d**	1-naph	**L1**	**3d**	99	87
8	Dioxane	**1b**	Ph	**L2**	**3b**	99	76
9	Dioxane	**1b**	Ph	**L3**	**3b**	93	76
10	Dioxane	**1b**	Ph	**L4**	**3b**	99	58

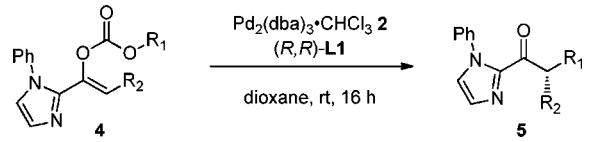
[a] Reactions performed using 0.2 mmol of substrate, 2.5 mol % **2**, and 6 mol % **Ln** in 1 mL of solvent at ambient temperature for 16 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. n.d. = not determined.



carbonates[8] (**4a**−**d**) participate in the reaction to generate 2-acylimidazole products **5a**−**d** in high yield and high ee (entries 2−5). Aryl and alkyl substitution on the enol carbonate are also tolerated (entries 6−9). The mild reaction conditions also permit the presence of alkynes (entry 6) and heteroaromatic substituents (entry 9). A variety of *O*-protected α-hydroxyketones can also be generated in good yield and ee using **L2**. To demonstrate the scalability of this process, reaction of enol carbonate **1b** was performed on a 2 mmol scale using just 1 mol % **2** and 2.5 mol % **L1** to generate product **3b** in 97% yield and 94% ee (entry 13).[9]

Our attention next turned to conversion of the 2-acylimidazole products to the corresponding carboxylic acid or ketone derivatives. While acyl transfer reactions of 2-acylimidazoles are well precedented,[10] we were unsure whether the transformations could be performed without racemizing the α-keto stereocenter. We were delighted to find that hydrolysis of the imidazole under standard

Table 2. Reactions of Different Imidazole Enol Carbonates

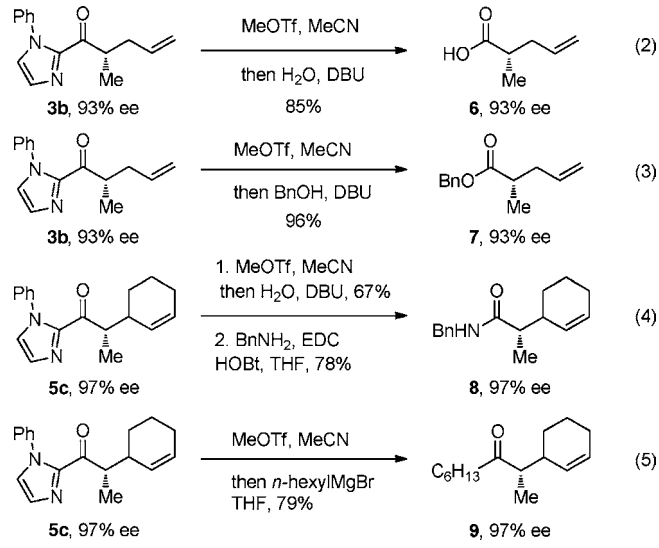


entry[a]	4	R^1	R^2	5	Yield (%)[b]	dr[c]	ee (%)[d]
1	**1b**		Me	**3b**	96		92
2	**4a**		Me	**5a**	95		92
3	**4b**		Me	**5b**	69	>95:5	>99
4	**4c**		Me	**5c**	91	>95:5	97
5[e,f]	**4d**		Me	**5d**	80[j]		46
6	**4e**			**5e**	91		93
7	**4f**			**5f**	75		94
8	**4g**		Ph	**5g**	99	>95:5	86
9	**4h**			**5h**	98	>95:5	97
10[g,h]	**4i**		OMOM	**5i**	85		71
11[g]	**4j**		OBn	**5j**	89		73
12[g]	**4k**		OTBDMS	**5k**	54	10:1	>99
13[i]	**1b**		Me	**3b**	97		94

[a] Unless otherwise noted, reactions were performed using 0.2 mmol substrate, 2.5 mol % **2**, and 6 mol % **L1** in 1 mL of solvent at ambient temperature for 16 h. [b] Isolated yields. [c] Determined by ^{1}H analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Reaction run for 48 h. [f] **L4** was employed. [g] **L2** was employed. [h] Reaction time was 30 min. [i] Performed on a 2 mmol scale with 1 mol % **2** and 2.5 mol % **L1** for 18 h. [j] 10:1 mixture *trans/cis* diene.

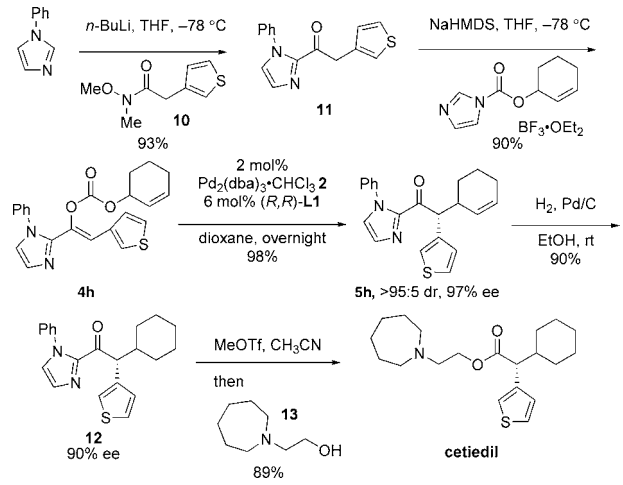
conditions (treatment with MeOTf in MeCN followed by addition of H_2O and DBU) gave carboxylic acid **6** in 85% yield with complete retention of stereochemistry (eq 2). In a similar fashion, 2-acylimidazole **3b** was converted to the benzyl ester derivative in 96% yield (eq 3). During our derivatization studies we found that direct conversion of the 2-acylimidazoles to amides or thioesters gave racemic products; converting the 2-acylimidazole first to the acid and then to the amide prevents racemization (eq 4). Conversion of imidazole ketone **5c** to the corresponding alkyl ketone by treatment of the methylated imidazole with *n*-hexylmagnesium bromide also proceeded smoothly to give ketone **9** in good yield (eq 5). Synthesizing α-chiral aliphatic ketones using this methodology circumvents the otherwise difficult alkylation of unsymmetrical ketones where regioselective enolization is challenging.

The synthetic utility of this new methodology is demonstrated by the concise synthesis of cetiedil (Scheme 1). Cetiedil is currently used clinically in racemic form for the treatment of vascular disease.[11] While enantiomerically pure cetiedil is generally obtained by fractional crystallization,[12] one asymmetric synthesis has been reported.[13] Ours begins with acylation of 1-phenylimidazole with Weinreb amide **10** to give 2-acylimidazole **11**. Formation of enol carbonate **4i** by *O*-acylation of the sodium enolate, followed by decarboxylative allylic alkylation of **4i** generates 2-acylimidazole **5i** in 98% yield and 97% ee. Hydrogenation of the double bond in **5i** gives ketone **12** in 90% yield and 90% ee.[14] Treatment of **12**



with methyl triflate and then amino alcohol **13** produces cetiedil in 89% yield and 90% ee.

Scheme 1. Synthesis of Cetiedil



In summary, we report the synthesis of highly enantioenriched 2-acylimidazoles by palladium-catalyzed decarboxylative asymmetric allylic alkylation of 2-imidazolo-substituted enol carbonates. The absolute configuration of the products of alkylation were established by comparison of carboxylic acid **6**[15] and our synthetic cetiedil[13] to known materials. In contrast to previously reported methods, the catalytic asymmetric alkylation methodology presented herein is quite general in scope for both the allylic electrophile and enolate nucleophile. The enantioenriched 2-acylimidazole products can easily be converted to the corresponding carboxylic acid, ester, amide, and ketone derivatives with complete retention of the enantiopurity.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Grant GM33049, for their generous support of our programs. K.L. thanks the Deutscher Akademischer Austausch Dienst (DAAD) for a fellowship. D.J.M. thanks the NIH for a postdoctoral fellowship (F32 GM093467-01).

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

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(8) Isomerically pure (*Z*)-enol carbonates (>95:5 *Z*/*E* as determined by ^{1}H NMR analysis) were generally synthesized as seen in Scheme 1.

(9) Lower catalyst loadings were not explored.

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JA103771W