

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

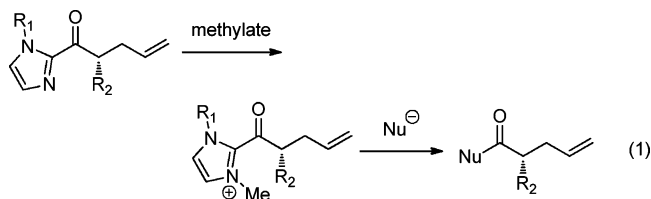
Barry M. Trost,* Konrad Lehr, David J. Michaelis, Jiayi Xu, and Andreas K. Buckl

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received May 3, 2010; E-mail: bmtrost@stanford.edu

The stereocontrolled alkylation of carbonyl compounds is a staple reaction in organic synthesis for the construction of highly enantio-enriched 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.



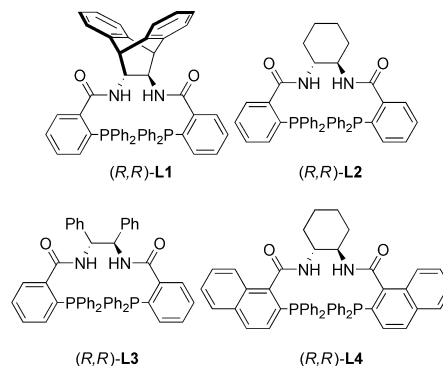
Our initial studies focused on the decarboxylative allylic alkylation reaction of allyl enol carbonates **1** catalyzed by Pd₂(dba)₃·CHCl₃ (**2**) and **L1** (Table 1, entries 1–4). While the reaction proceeded in a number of solvents, conducting it in dioxane generated alkylated product **3a** with 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 ₂ Cl 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.



carbonates⁸ (**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 predated,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

References

- (1) For reviews, see: (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chapter 1, pp 83–110. (b) Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chapter 3, pp 213–274.
- (2) For recent reviews, see: (a) Prabhat; Qin, H. *Tetrahedron* **2000**, *56*, 917–947. (b) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219–235.
- (3) For selected examples of catalytic asymmetric alkylations of ketones and derivatives, see: (a) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829–8830. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *Tetrahedron* **2000**, *56*, 179–185. (c) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *127*, 62–63. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (e) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2006**, *71*, 8651–8654. (f) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701–3705. (g) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357. For an example of an intramolecular alkylation of aldehydes, see: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2003**, *126*, 450–451.
- (4) For reviews on the alkylation of glycine derivatives by chiral phase-transfer catalysis, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (b) Jew, S.; Park, H. *Chem. Commun.* **2009**, *46*, 7090–7103.
- (5) Andrus, M. B.; Christiansen, M. A.; Hicken, E. J.; Gainer, M. J.; Bedke, D. K.; Harper, K. C.; Mikkelsen, S. R.; Dodson, D. S.; Harris, D. T. *Org. Lett.* **2007**, *9*, 4865–4868.
- (6) Andrus, M. B.; Harper, K. C.; Christiansen, M. A.; Binkley, M. A. *Tetrahedron Lett.* **2009**, *50*, 4541–4544.
- (7) Ohta, S.; Hayakawa, S.; Nishimura, K.; Okamoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 1058–1069, and references therein.
- (8) Isomerically pure (Z)-enol carbonates (>95:5 Z/E as determined by ¹H NMR analysis) were generally synthesized as seen in Scheme 1.
- (9) Lower catalyst loadings were not explored.
- (10) For selected examples of the utility of 2-acylimidazoles in their conversion to other groups such as acids, esters, ketones, etc.; see: (a) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (b) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351–3354. (c) Davies, D. H.; Haire, N. A.; Hall, J.; Smith, E. H. *Tetrahedron* **1992**, *48*, 7839–7856. (d) Bakhtiar, C.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 239–243.
- (11) Schmidt, W. F., III; Asakura, T.; Schwartz, E. *J. Clin. Invest.* **1982**, *69*, 589–594.
- (12) Roxburgh, C. J.; Ganellin, C. R.; Shiner, M. A. R.; Benton, D. C. H.; Dunn, P. M.; Ayalew, Y.; Jenkinson, D. H. *J. Pharm. Pharmacol.* **1996**, *48*, 851–857.
- (13) Davies, H. M. L.; Walji, A. M.; Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981–4983.
- (14) The drop in the enantioselectivity upon hydrogenation of **5i** is reflective on the conversion of both diastereomers in **5i** to **12**.
- (15) Riley, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 1171–1174.

JA103771W