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Published on Web 12/17/2003

Catalytic Asymmetric Intramolecular α-Alkylation of Aldehydes

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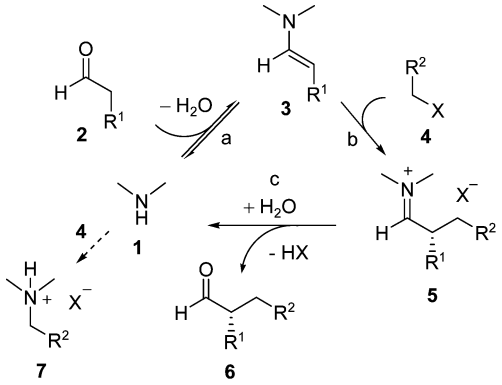
α-Alkylations of carbonyl compounds are central carbon−carbon-*σ*-bond forming reactions in organic synthesis.[1] Asymmetric variants generally rely on the use of chiral auxiliaries, and a variety of efficient examples have been reported in the last three decades.[2−5] Despite its potential as a broadly useful synthetic methodology, the development of a general catalytic asymmetric α-alkylation reaction has proven extremely challenging, and the only two reported strategies are limited in scope. For example, the very useful asymmetric phase-transfer catalysis approach is most commonly applied in the synthesis of α-amino acids via alkylation of a glycine derivative.[6] The other notable but indirect strategy developed by Koga et al.[7] uses chiral oligoamines as catalysts for the α-benzylation of preformed cyclohexanone lithium enolates. Although chiral α-branched aldehydes are particularly valuable synthetic intermediates, neither direct nor indirect catalytic asymmetric α-alkylations of aldehydes are known. Here, we describe the first, efficient, and highly enantioselective intramolecular direct aldehyde α-alkylation reactions.

Even stoichiometric α-alkylations of preformed aldehyde enolate equivalents are very difficult to control, and several side reactions usually occur. For example, in the reactions of metal enolates or enamines of aldehydes with alkyl halides, self-aldolization, Cannizzaro or Tischchenko reactions, and N- or O-alkylations are competing processes.[8,9] Designing a catalytic asymmetric α-alkylation of aldehydes is further complicated by the susceptibility of the nucleophilic Lewis- or Brønsted-base catalyst toward an unproductive alkylation reaction with the electrophile. In addition, racemization of the product could be a serious problem.

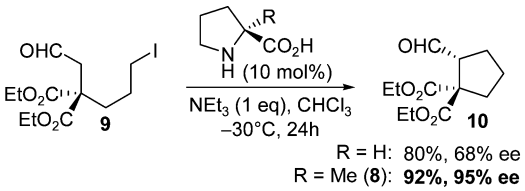
Based on our previous successful use of enamine catalysis as a powerful strategy in asymmetric synthesis,[10,11] we wondered whether this approach could be extended to a catalytic asymmetric α-alkylation reaction of aldehydes (or ketones). Fully aware of the potential benefits but also of the many difficulties we would likely encounter, we decided to pursue this formidable challenge. In our reaction design, we envisioned a catalytic cycle (eq 1) involving an initial reversible enamine formation from amine **1** and aldehyde **2** (a). Enamine intermediate **3** should then react with alkyl halide **4** to furnish iminium salt **5** (b), while the potential N-alkylation of the amine catalyst itself to give catalytically inactive tertiary ammonium salt **7** should not occur. Hydrolysis of salt **5** (c) would finally regenerate catalyst **1** and provide the α-branched aldehyde product (**6**) along with 1 equiv of acid HX to be trapped by stoichiometrically added base.

We initially investigated the intermolecular α-alkylation reaction of cyclohexanone and propionaldehyde with benzylbromide catalyzed by proline in the presence of triethylamine, but unsurprisingly we only identified products of proline benzylation. We then studied the intramolecular alkylation of aldehyde **9** under the same conditions and to our excitement found this reaction to furnish aldehyde **10** in good yield and promising 68% ee (eq 2). After optimizing the reaction conditions, and screening several proline derivatives and other amines as alternative catalysts, we found that



(1)

commercially available (*S*)-α-methyl proline (**8**) significantly improved both the rate and the enantioselectivity of the reaction. Treating aldehyde **9** with catalyst **8** (10 mol %) in chloroform at −30 °C in the presence of triethylamine furnished cyclopentane carbaldehyde **10** in excellent yield (92%) and enantioselectivity (95% ee) (eq 2).



(2)

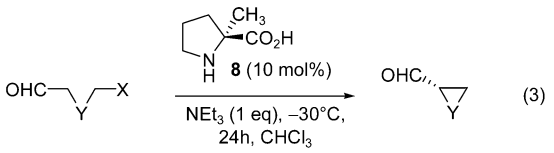
Next, we studied the scope of this novel reaction (eq 3, Table 1). Varying the leaving group (−I, −Br, −OTs) furnished product **10** in similar high enantioselectivities, although the cyclization of tosylate **12** was particularly slow. Replacing ethyl with benzyl groups as in ester **13** furnished the corresponding product (**14**) in almost identical enantioselectivity and yield. If structural isomer **15** was treated with catalyst **8**, aldehyde **16** was obtained in 93% yield and 83% ee. Running this reaction in mesitylene instead of chloroform further improved the enantioselectivity to 97% ee. Much to our delight, we found that extending this new reaction to the synthesis of heterocycles worked equally well. Thus, subjecting amino aldehyde **17** to the reaction conditions furnished (*S*)-*N*-tosyl prolinal (**18**) in high enantioselectivity. Furthermore, we were able to extend our methodology to alternative cyclization modes such as the 3-exo-tet cyclization of aldehyde **19** to cyclopropane **20** in high yield and enantioselectivity.

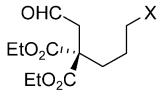
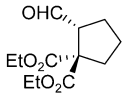
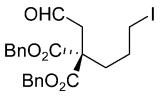
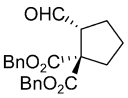
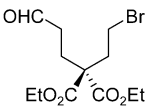
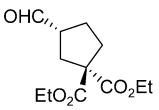
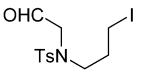
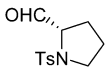
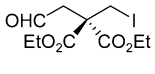
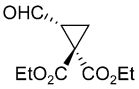
The ee's of the produced cyclic aldehydes were determined via conversion to the corresponding enones using an in situ Horner−Wadsworth−Emmons reaction followed by chiral stationary phase HPLC analysis.

The absolute configuration of prolinal **18** was determined by measuring the optical rotation of its known alcohol reduction product.[12] At this point, a detailed mechanistic explanation of the enantiodifferentiation appears premature. However, the results are

10.1021/ja0392566 CCC: $27.50

Table 1. (*S*)-α-Methyl Proline-Catalyzed Direct Asymmetric Intramolecular α-Alkylation of Aldehydes



Entry	Substrate	Product	Yield (%)	ee (%)[a]
(1)	 **9** (X = I)	 **10**	92[b]	95
(2)	**11** (X = Br)	**10**	90[c]	94
(3)	**12** (X = OTs)	**10**	20[d]	91
(4)	 **13**	 **14**	94	95
(5)	 **15**	 **16**	92[e] 93[c]	96 84
(6)	 **17**	 **18**	52[f]	91
(7)	 **19**	 **20**	70[e]	86

[a] Determined by chiral stationary phase HPLC analysis after in situ Horner−Wadsworth−Emmons olefination to the corresponding enone (e.g. $(MeO)_2POCH_2COMe$, LiOH). [b] At 0 °C, 5 mol % **8**, 89% yield and 91% ee was obtained. [c] 15 mol % **8**. [d] 20 mol % **8**, 48 h. [e] 20 mol % **8**, −15 °C, mesitylene, 216 h. [f] After in situ reduction to the corresponding alcohol ($NaBH_4$, MeOH).

consistent with related proline-catalyzed reactions and with previous mechanistic proposals.[10,13] The considerable increase in enantioselectivity observed by switching from (*S*)-proline to its α-methyl derivative **8** is remarkable. It has earlier been demonstrated that in proline-catalyzed aldolizations the *syn*- versus *anti*-enamine conformation plays an important role in the enantiodifferentiation.[13] The α-geminal disubstitution in catalyst **8** might shift this equilibrium toward the *anti*-enamine because of 1,3-allyllic strain interactions occurring in the corresponding *syn*-conformer. Ultimately, it may be this *anti*-preference which translates into the observed high enantioselectivity in the transition state. Exactly how the enantiodifferentiation occurs mechanistically remains to be determined. Currently, we speculate a triethylammonium carboxylate to be involved in the ionic activation of the leaving group in the cyclization.

In summary, we have discovered the first catalytic asymmetric α-alkylation of aldehydes. Our process furnishes chiral substituted cyclopentanes, cyclopropanes, and pyrrolidines in high yields and ee's. The catalyst is commercially available in both enantiomeric forms, and the reaction conditions are simple and practical. Most remarkably, racemization, aldolization, or catalyst alkylation do not occur to any significant extend, further illustrating the power, mildness, and profound selectivity of enamine catalysis.

Currently, we are expanding the scope of our new asymmetric alkylation to other cyclization modes and to an intermolecular variant. First results will be communicated in due course.

Acknowledgment. This paper is dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday. We thank Jo Van Betsbrugge of BioQuadrant Pharmaceutical Intermediates Inc., Canada, for the generous gift of proline derivatives. Support by the Max-Planck-Institut für Kohlenforschung and technical assistance by L. Goossen, A. Döhring, and H. Hinrichs is gratefully acknowledged.

Supporting Information Available: Experimental procedures, spectra, and HPLC data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0392566