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A New Strategy for Extending *N*-Acyl Imides as Chiral Auxiliaries for Aldol and Diels–Alder Reactions: Application to an Enantioselective Synthesis of α-Himachalene**

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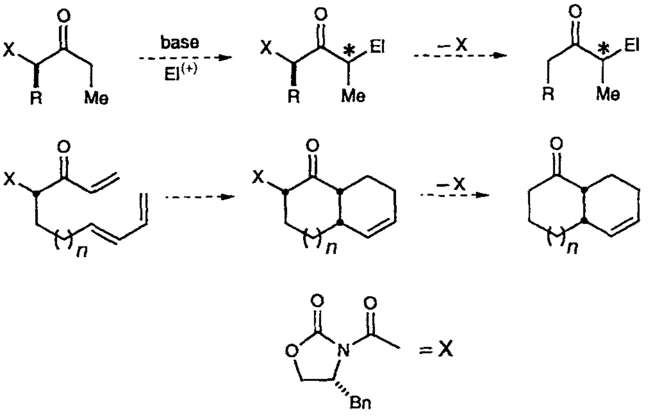
Jeffrey S. Johnson, and Eileen A. Shaughnessy

The development of enantioselective transformations involving the ketone functional group continues to be a problem of general interest in asymmetric synthesis due to the ubiquity of this functionality. While chiral Lewis acids have been employed to promote enantioselective aldol and Diels–Alder reactions of carboxylic acid derivatives and aldehydes, stereocontrol is generally low in reactions of ketones due to the lack of differentiation in Lewis acid coordination to the two nonbonding electron pairs of the carbonyl group.[1] One strategy for creating a stereochemical bias in ketone-derived enolate–electrophile reactions [Eq. (1)] or in the transformations of α,β-unsaturated ketones such as the Diels–Alder reaction [Eq. (2)] has been developed. In these processes, a stereogenic center, created by the incorporation of the removable substituent X, is positioned proximal to the trigonal carbon centers undergoing reaction, thus establishing a diastereofacial bias for the transformation. The implementation of this strategy for enolates and enolsilanes of α-trialkylsilyl ketones [Eq. (1), X = SiR_3] has been reported by Enders and Lohray,[2, 3] while Heathcock and Masamune have demonstrated that the aldol and Diels–Alder reactions of α-alkoxyketones [Eqs. (1) and (2), X = OR] are highly diastereoselective.[4]



(1)

(2)

Here we define the removable auxiliary X = COX_c (X_c = 4-benzyl-2-oxazolidinon-3-yl), which can be used in the previously described enolate bond constructions and combined with a mild hydrolysis/decarboxylation procedure to extend the utility of β-ketoimides[5] to the production of enantiopure ketones [Eq. (1)]. We also demonstrate that this strategy is applicable to the implementation of enantioselective Diels–Alder reactions [Eq. (2), X = COX_c).

We have previously demonstrated that the β-ketoimide **1**[6] undergoes metal ion dependent stereoselective *syn*-[7] and *anti*-aldol[6] reactions. In addition, the titanium enolate[8] derived

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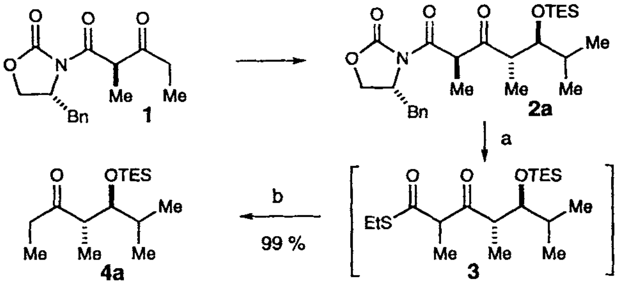
from **1** has also been shown to undergo diastereoselective orthoester acylation.[9]

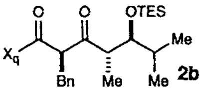
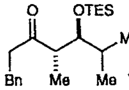
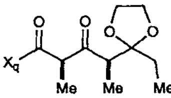
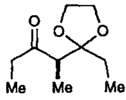
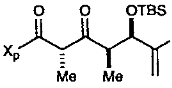
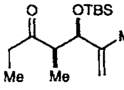
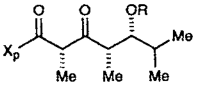
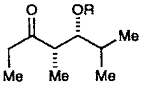
The focus of the current investigation has been the development of a mild decarboxylation process that might be applied to the enolate-derived reaction products that are prone to epimerization and/or elimination.[10] A successful solution to this transformation is transesterification with ethanethiolate[11] followed by silver(I)-promoted hydrolysis/decarboxylation[12] of the resulting thioester (Scheme 1).



Scheme 1. Thiolate displacement, hydrolysis, and decarboxylation of β-oxoimide **2a**[6]: a) EtSH, KH, THF, 25°C; b) AgNO$_3$, 2,6-lutidine, THF/H$_2$O (5/1), 25°C. TES = triethylsilyl.

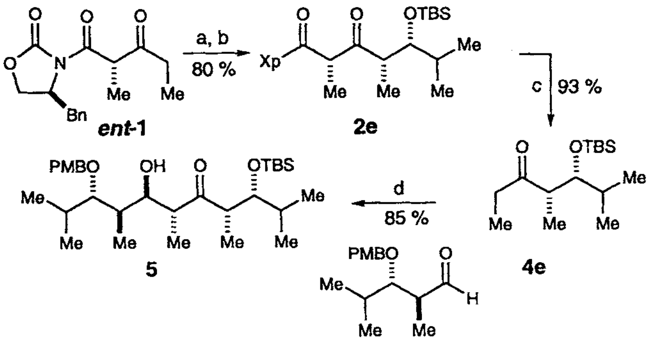
Treatment of **2a** with potassium ethanethiolate afforded a mixture of C_α-diastereomeric β-ketothioesters **3**.[13] Subjecting thioesters **3** to silver(I)-promoted hydrolysis and subsequent decarboxylation at ambient temperature provided ethyl ketone **4a** over the course of 48 hours. In most instances the reaction time may be reduced without compromising yield by mild heating during the hydrolysis step (70°C, 3 h). The two steps may be merged into a single-flask operation (see Experimental Section). The decarboxylation of β-ketoimide-derived aldol and orthoester acylation adducts **2a**–**2f** was investigated using this procedure (Table 1). The mild reaction conditions accommodate the presence of ketal, silyl ether, alkene, and acetate functionalities.

Table 1. One-flask decarboxylation of representative β-ketoimide adducts[a].

Imide	Product	Yield [%][b]	t [h][c]
 **2b**	 **4b**	98	24
 **2c**	 **4c**	79 74	24 3[d]
 **2d**	 **4d**	88	48
 **2e**, R = TBS	 **4e**	93 92	48 3[d]
2f, R = Ac	**4f**	83	48

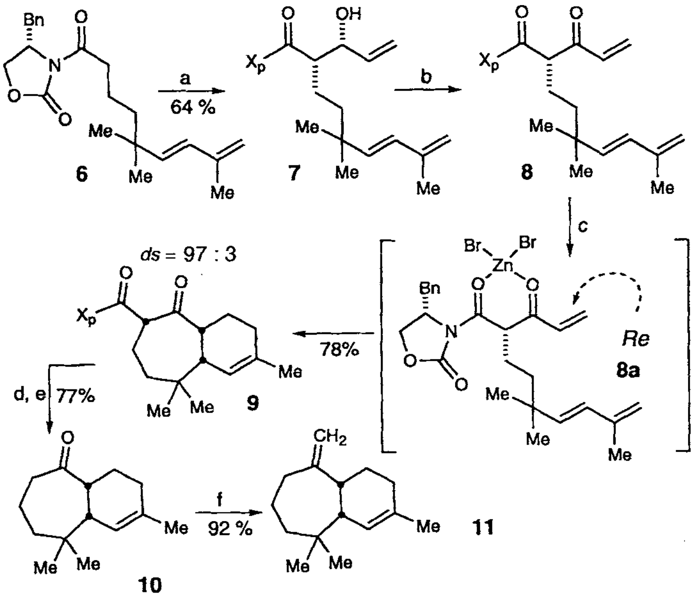
[a] X$_p$ = (S)-4-benzyl-2-oxazolidinon-3-yl, X$_q$ = (R)-4-benzyl-2-oxazolidinon-3-yl, TBS = $tert$-butyldimethylsilyl. [b] Yield after purification. [c] Reaction time for the hydrolysis step. [d] Hydrolysis run at reflux.

These ketone decarboxylation products are useful building blocks for the rapid synthesis of extended polypropionate chains.[14] In the example shown in Scheme 2, polypropionate **5**, containing six stereocenters, was synthesized in four steps (63% yield) from β-ketoimide **1**; all stereocenters were formed with a combined diastereoselectivity exceeding 95%.[14e]



Scheme 2. Strategy for the rapid assembly of polypropionate chains. a) 1. TiCl$_4$, Et$_3$N, 0°C, 2. iPrCHO, −78°C; b) TBSOTf, 2,6-lutidine, −78°C; c) 1. EtSH, KH, 2. AgNO$_3$, 2,6-lutidine, H$_2$O; d) $c$hex$_2$BCl, Et$_3$N, −78°C. OTf = trifluoromethanesulfonate, PMP = 4-methoxybenzyl.

This auxiliary-based methodology can be applied to achieve control of the absolute stereochemistry in the Diels–Alder process [Eq. (2)]. In this context, we investigated an intramolecular Diels–Alder reaction that comprises the pivotal bond construction in an enantioselective synthesis of the sesquiterpene α-himachalene (**11**).[15] Dienimide **6**, prepared in five steps from 3,3-dimethyl-4-propenal, underwent a highly diastereoselective boron-mediated aldol reaction with acrolein to afford the allylic alcohol **7** as the sole isomer (Scheme 3).[16] Compound **7** was subjected to Parikh–Doering oxidation[17] and the resulting trienone **8** was treated with ZnBr$_2$ (0°C, CH$_2$Cl$_2$, 1.5 h) to effect cycloaddition (78% yield, two steps) to the desired crystalline *endo* adduct **9** (97:3 diastereoselectivity), which was isolated as



Scheme 3. Enantioselective synthesis of α-himachalene (**11**). a) 1. Bu$_2$BOTf, iPr$_2$NEt, isoprene, 0°C, 2. acrolein, −78°C; b) SO$_3$·pyridine, DMSO/CH$_2$Cl$_2$, iPr$_2$NEt, −10°C; c) ZnBr$_2$, 0°C; d) LiSEt; e) AgNO$_3$, 2,6-lutidine, THF/H$_2$O, 70°C; f) [Cp$_2$Ti(μ-Cl)(μ-CH$_2$)AlMe$_2$], −40°C.

a single diastereomer by chromatography. The sense of asymmetric induction in this cycloaddition is consistent with a Lewis acid catalyzed Diels–Alder reaction on the *s-cis* $ZnBr_2$ complex **8a**.

In analogy to previous experiments, Diels–Alder adduct **9** was transformed to the corresponding β-ketothioester in 90% yield and smoothly decarboxylated (70 °C, 24 h) to afford ketone **10** in 86% yield without epimerization at the ring fusion. The synthesis was completed by treatment of **10** with Tebbe reagent[18] to afford synthetic α-himachalene (**11**) (92% yield), whose spectroscopic and analytical data are identical in all respects to literature values (^{1}H NMR, IR, TLC, $[\alpha]_D$).[15]

The removable auxiliary $X = COX_c$ described here should prove useful in enantioselective ketone-based bond constructions. Although the methodology has been highlighted with aldol and Diels–Alder reactions, absolute stereochemical control of other transformations such as the Michael reaction should also be possible. Studies extending the scope of these concepts are currently underway.

Experimental Section

General one-flask procedure for the decarboxylation of β-ketoimides: A stirred suspension of KH (1.2 mmol) in THF (10 mL) under argon was charged with EtSH (1.3 mmol) and gas evolved. The white suspension was stirred for 1 h before a solution of β-oxoimide (1 mmol) in THF (10 mL) was added by cannula. The reaction mixture was stirred until the starting material had been consumed. To the reaction mixture was added water (4 mL) and 2,6-lutidine (10 mmol), followed by $AgNO_3$ (2.5 mmol). The reaction mixture was protected from light and stirred for two days. The pale yellow suspension was filtered through Celite with ether, and the organic solution was extracted between ether (50 mL) and aqueous $CuSO_4$ solution (50 mL). The ether layer was separated, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel using an appropriate solvent mixture provided pure ketone.

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One-Component Catalysts for Thermal and Photoinduced Ring Opening Metathesis Polymerization

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New generations of stereospecific olefin polymerization catalysts have catapulted the polymer industry into a new area. A large variety of thermoplastic materials, based on α-olefins, of well-defined tacticity and block length are expected to be commercialized in the near future.[1] A similar development can be foreseen for thermoset materials. In this respect ring opening metathesis polymerization (ROMP)[2] offers new types of polymers with attractive mechanical and electrical properties. Currently applied industrial catalysts for ROMP are multicomponent systems based on early transition metal complexes and water-sensitive alkylaluminum cocatalysts. In the mid 1980s the first well-defined, one-component catalysts for ROMP were developed by Osborn (e.g., $[WCl_2(=CHCMe_3)(OR)_2]$)[3] and Schrock (e.g., $[Mo(=CHCMe_3)(=NAr)(OR)_2]$).[4] However, these catalysts are air- and moisture-sensitive as well, and sparsely tolerate monomers bearing protic substituents, fillers, or other additives.

In contrast to early transition metal catalysts, ruthenium- and osmium-based complexes are water-stable and possess remarkable tolerance towards most functional groups.[5] Therefore, the use of these catalysts goes far beyond the classical scope of olefin-metathesis reactions.

When we started our work in the field of ROMP by studying the reactivity of $[Ru(H_2O)_6]^{2+}$, we were able to prepare polymers and copolymers from cyclic olefins containing a large variety of functional groups.[6] Using the concept of photoinduced arene displacement, we developed the first photocatalysts for ROMP (PROMP) by generating $[Ru(H_2O)_6]^{2+}$ from $[Ru(\eta^6\text{-arene})_2]^{2+}$.[7, 8] A disadvantage of these catalysts is their cationic character, which restricts their applicability to polar environments, and their moderate reactivities. Therefore, we focused our attention on more soluble and more active arene complexes of ruthenium and osmium.

In 1992 Grubbs et al. reported the synthesis of the first well-defined, metathesis-active ruthenium–carbene complex by ring opening of a substituted cyclopropene with $[RuCl_2(PPh_3)_3]$.[9]

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