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Hypervalent Iodine |*Hot Paper*|

Diastereoselective Radical Hydroacylation of Alkylidenemalonates with Aliphatic Aldehydes Initiated by Photolysis of Hypervalent Iodine(III) Reagents

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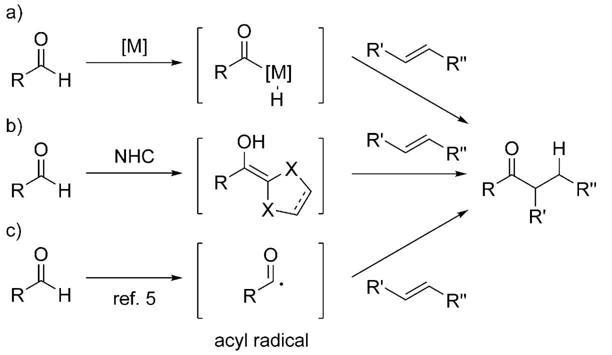
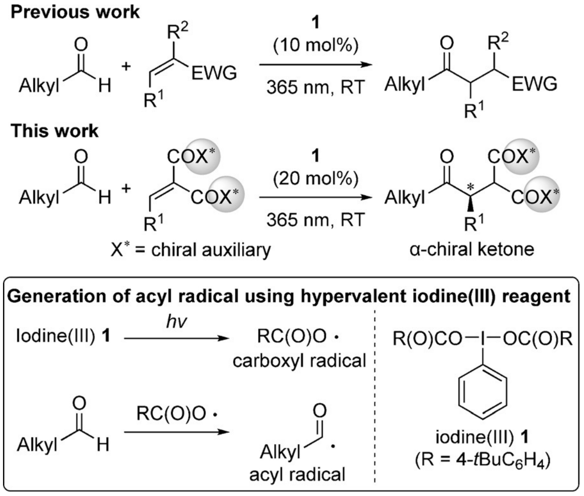
Abstract: Diastereoselective radical hydroacylation of chiral alkylidenemalonates with aliphatic aldehydes is realized by the combination of a hypervalent iodine(III) reagent and UV-light irradiation. The reaction is initiated by the photolysis of hypervalent iodine(III) reagents under mild, metal-free conditions, and is the first example of diastereoselective addition of acyl radicals to olefins to afford chiral ketones in a highly stereoselective fashion. The obtained optically active ketones are useful chiral synthons, as exemplified by the short formal synthesis of (−)-methyleneolactocin.

Intra- or intermolecular coupling between aldehydes and olefins is a useful method for the construction of synthetically useful building blocks in organic synthesis. Among them, metal-catalyzed hydroacylation[1] and the Stetter reaction catalyzed by *N*-heterocyclic carbenes (NHCs)[2] have proven to be powerful strategies for the preparation of various ketone compounds from aldehydes and olefins (Scheme 1 a and b). Especially in recent years, the development of asymmetric metal-catalyzed hydroacylation[3] and asymmetric Stetter reactions[4] to prepare chiral ketones has been the subject of intensive research, whereas radical hydroacylation through generation of acyl radicals from aldehydes also has the potential to become an attractive approach to the atom-economic synthesis of ketones (Scheme 1 c).[5] However, this approach has been less investigated than the metal-catalyzed hydroacylation or NHC-catalyzed Stetter reaction, and, to our knowledge, stereoselective addition of acyl radicals to olefins for the construction of chiral ketones has not been reported to date.



Scheme 1. Hydroacylation of olefins with aldehydes: a) Metal-catalyzed hydroacylation; b) NHC-catalyzed Stetter reaction; c) radical hydroacylation.

Recently, we reported the photolytic radical hydroacylation of electron-deficient olefins with aldehydes in the presence of a catalytic amount of hypervalent iodine(III) reagent **1** (Scheme 2).[5g,6] In this approach, acyl radicals can be easily generated from aldehydes induced by the photolysis of hypervalent iodine(III) reagent **1** to form a carboxyl radical, and subsequent addition of the radicals to olefins gives ketones under mild, metal-free conditions.[7] Our reaction system also enables the use of various aliphatic aldehydes, which have rarely been employed with success in either the metal-catalyzed hydroacylation or the NHC-catalyzed Stetter reaction.[8] To demonstrate the further utility of our approach, we have become interested in the possibility of diastereoselective addition of acyl radicals to olefins by installation of a chiral auxiliary on olefins. Herein, we report the first diastereoselective radical hydroacylation of



Scheme 2. Radical hydroacylation of olefins with aldehydes initiated by the photolysis of hypervalent iodine(III) reagents.

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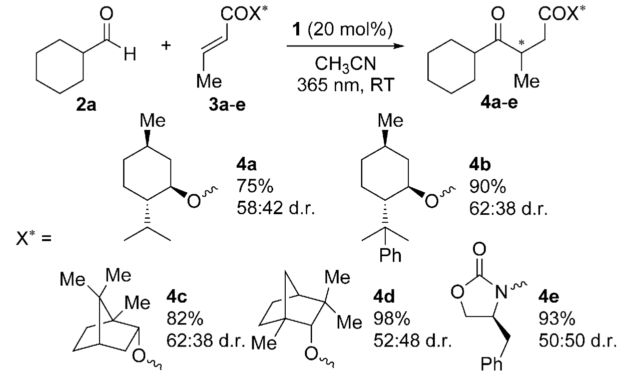
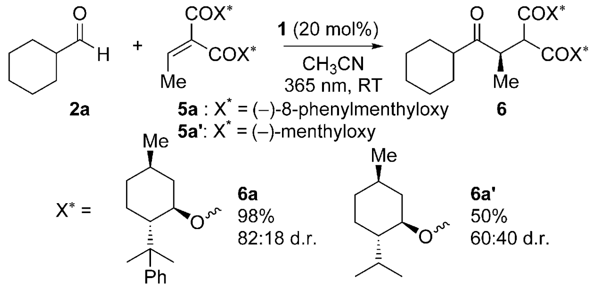
olefins with aliphatic aldehydes for the stereocontrolled synthesis of chiral ketones.

We first examined the diastereoselective radical hydroacylation between cyclohexanecarboxaldehyde **2a** with various chiral crotonate derivatives **3a-e** containing one chiral auxiliary on the ester moiety, derived from (−)-menthol, (−)-8-phenylmenthol, (−)-borneol, (+)-fenchol, or (*S*)-4-benzyl-2-oxazolidinone (Scheme 3). In the presence of a catalytic amount of **1** under UV light, the corresponding ketones **4a**–**e** were obtained in moderate to high yields, albeit with low diastereoselectivities.



Scheme 3. Radical hydroacylation of chiral crotonates.

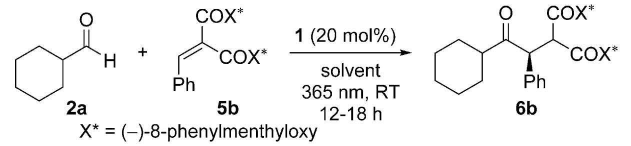
We then used an alkylidenemalonate **5a**, which incorporates two (−)-8-phenylmenthyloxy groups on the ester moieties, for this reaction.[9] Fortunately, use of **5a** successfully improved the diastereoselectivity, affording the corresponding ketone **6a** in quantitative yield with 82:18 d.r. (Scheme 4). It should be noted that the bis(menthyloxy) analogue **5a′** [X* = (−)-menthyloxy] led to significantly lowered yield and diastereoselectivity (50 % yield, 64:36 d.r.).



Scheme 4. Radical hydroacylation of chiral alkylidenemalonates.

In an effort to improve the diastereoselectivity, further optimization of the reaction conditions was investigated in various solvents (Table 1). A survey of solvents indicated that the mixed solvent system CH_3CN/CH_2Cl_2 was among the best in terms of diastereoselectivity (Table 1, entry 6). When the reaction was performed under visible light ($\lambda = 400$ nm), a slightly decreased yield and diastereoselectivity were obtained (Table 1, entry 7 vs. 6).

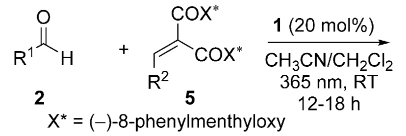
Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	Yield [%][b]	d.r.[c]
1	CH_3CN	98	82:18
2	CH_2Cl_2	80	87:13
3	benzene	98	91:9
4	toluene	98	90:10
5	C_6F_6	96	90:10
6	CH_3CN/CH_2Cl_2	91	92:8
7[d]	CH_3CN/CH_2Cl_2	65	87:13

[a] The reaction of **2a** (0.225 mmol) and **5b** (0.15 mmol) was conducted in the presence of **1** (20 mol %) in a solvent (2.4 M) with irradiation by UV light ($\lambda = 365$ nm). [b] Determined by 1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Determined by ^{1}H NMR analysis. [d] Reaction performed with irradiation by visible light ($\lambda = 400$ nm).

Table 2. Substrate scope.[a]

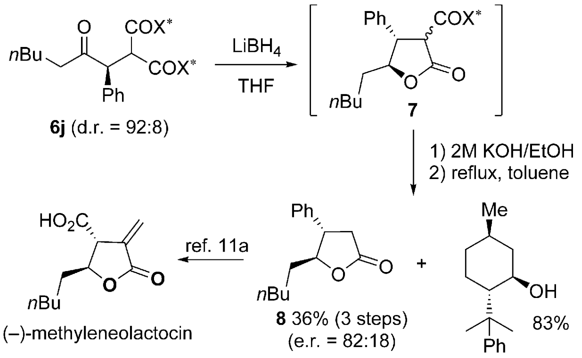


Entry	R^1	R^2	Yield [%][b]	d.r.[c]
1	Cy (**2a**)	Me (**5a**)	89 (**6a**)	82:18
2	Cy	Ph (**5b**)	83 (**6b**)	92:8
3	Cy	CF_3 (**5c**)	48 (**6c**)	84:16
4	Cy	4-FC_6H_4 (**5d**)	91 (**6d**)	88:12
5	Cy	4-ClC_6H_4 (**5e**)	65 (**6e**)	89:11
6	Cy	4-MeC_6H_4 (**5f**)	65 (**6f**)	89:11
7	CH_2*i*Pr (**2b**)	Ph	87 (**6g**)	90:10
8	*n*Pr (**2c**)	Ph	80 (**6h**)	88:12
9	*n*Bu (**2d**)	Ph	85 (**6i**)	89:11
10	*n*Pentyl (**2e**)	Ph	93 (**6j**)	92:8
11	*n*C_8H_{17} (**2f**)	Ph	84 (**6k**)	86:14
12[d]	CH(Et)$_2$ (**2g**)	Ph	82 (**6l**)	90:10

[a] The reaction of **2** (0.225 mmol) and **5** (0.15 mmol) was conducted in the presence of **1** (20 mol %) in 1:1 CH_3CN/CH_2Cl_2 (2.4 M) with irradiation by UV light ($\lambda = 365$ nm). [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of crude mixture. [d] 4 Equivalents of **2g** were employed without solvent for 48 h.

With the optimized conditions in hand, we investigated the substrate scope of the reaction (Table 2). In the presence of a catalytic amount of **1**, the reaction of **2a** (R^1 = cyclohexyl) with various alkylidenemalonates **5** gave the corresponding products **6a**–**f** in moderate to high yields with good diastereoselectivities. Use of 2-trifluoromethyl malonate **5c** ($R^2 = CF_3$) gave the α-trifluoromethyl ketone **6c** in 48 % yield with 84:16 d.r. (Table 2, entry 3). Introduction of electron-donating and electron-withdrawing substituents on the 2-aryl group of **5b** did not significantly affect the yields and diastereoselectivities (Table 2, entries 4–6). The reaction of various linear or branched aliphatic aldehydes **2b**–**g** with **5b** (R^2 = Ph) proceeded smoothly to give the corresponding ketones **6g-l** in excellent yields with good diastereoselectivities (Table 2, entries 7–12).[10]

The synthetic utility of the present reaction was successfully demonstrated in the short formal synthesis of (−)-methyleneolactocin (Scheme 5),[11–13] which has potent antibacterial and antitumor activities. First, treatment of ketone **6j** with $LiBH_4$ resulted in the formation of γ-butyrolactone **7**. Then, hydrolysis of **7** and subsequent decarboxylation afforded γ-butyrolactone **8** in 36% overall yield, which can be converted to (−)-methyleneolactocin.[13a] Although the stereoselectivity of the product was slightly decreased, γ-butyrolactone **8** was obtained in only three steps from ketone **6j**. It is also worth noting that during this transformation, (−)-8-phenylmenthol was successfully recovered in 83% yield.



Scheme 5. Formal total synthesis of (−)-methyleneolactocin.

Based on the observed stereochemistry of the product, a proposed explanation for this diastereoselectivity is depicted in Figure 1. At the addition step of the acyl radical to the olefin, effective shielding of one diastereotopic face of alkylidenemalonates might be realized by the phenyl group of one chiral auxiliary, which would explain the low diastereoselectivity achieved when using **5a′**.

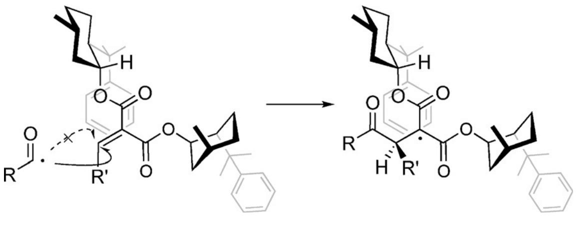


Figure 1. Proposed transition state model for explanation of diastereoselectivity.

In summary, we developed a diastereoselective radical hydroacylation of chiral alkylidenemalonates with aldehydes in combination with a hypervalent iodine(III) reagent and UV-light irradiation. This process represents the first example of diastereospecific addition of acyl radicals to olefins for the synthesis of chiral ketones in a highly stereoselective fashion. Further application of the present photoreaction of hypervalent iodine(III) reagent, particularly for the development of new carbon–carbon bond formation reactions, is under investigation.

Experimental Section

In a reaction tube containing benzylidenemalonate **5b** (0.15 mmol), hypervalent iodine(III) reagent **1** (0.03 mmol) and cyclohexanecarboxaldehyde **2a** (0.225 mmol) were mixed in a 1:1 CH_3CN/CH_2Cl_2 solvent mixture (2.4 M with regard to **5b**) under argon atmosphere. The mixture was irradiated with UV light ($\lambda = 365$ nm) with stirring for 12 h. After completion of the reaction, the solvent was removed under reduced pressure. The diastereoselectivity of ketone **6b** was determined by ^1H NMR analysis of the crude mixture. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20:1 to 4:1 as eluent) to afford ketone **6b** (91.1 mg, 0.124 mmol, 83% yield, d.r. = 92:08); $[\alpha]_D^{23} = 137.97$ ($c = 1.3$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$–7.07 (15H, m), 4.80 (1H, dt, $J = 11.0$, 4.5 Hz), 4.72 (0.08H, m), 4.55 (1H, dt, $J = 11.0$, 4.5 Hz), 4.47 (0.92H, d, $J = 11.5$ Hz), 3.95 (1H, m), 2.43 (1H, m), 2.12 (1H, m), 1.94 (1H, m), 1.78 (2H, m), 1.64–1.45 (6H, m), 1.42–1.05 (24H, m), 0.97–0.86 (2H, m), 0.82 (3H, d, $J = 6.5$ Hz), 0.67 (1H, m), 0.60 (3H, d, $J = 6.5$ Hz), 0.52–0.43 ppm (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$; data given for major isomer): $\delta = 210.4$, 168.4, 167.6, 150.6, 150.4, 134.1, 129.8, 128.9, 128.1, 126.1, 126.0, 125.5, 125.3, 76.6, 76.2, 56.3, 55.4, 50.8, 50.3, 49.9, 41.1, 40.6, 40.3, 34.6, 34.2, 31.5, 31.3, 31.0, 29.5, 28.8, 28.6, 27.2, 27.1, 26.0, 25.8, 25.4, 25.1, 23.1, 21.8, 21.5 ppm; IR (neat): $\tilde{\nu} = 2929$, 1739, 1707, 1594, 1264 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{49}H_{64}NaO_5$: 755.4646 $[M + Na^+]$; found: 755.4653.

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Keywords: hydroacylation · hypervalent iodine · radical reactions · diastereoselectivity · photolysis

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