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Copper Hydride Catalyzed Reductive Claisen Rearrangement

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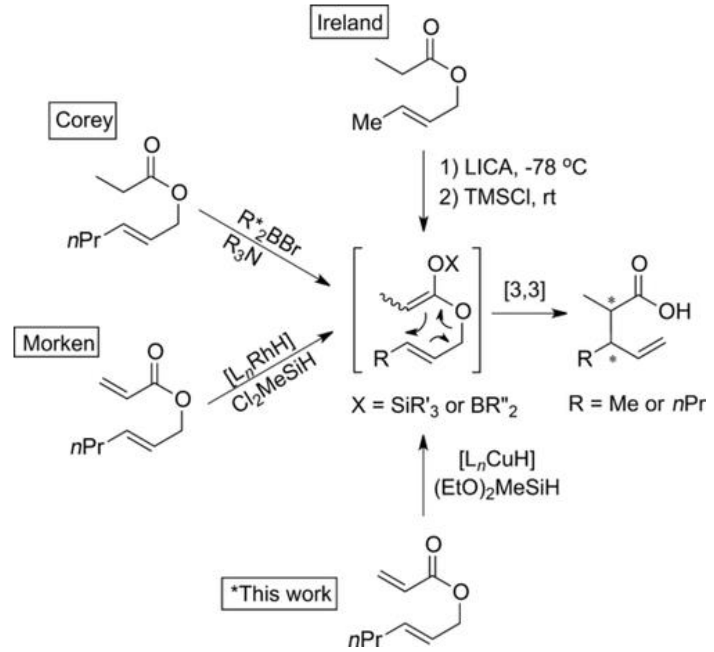
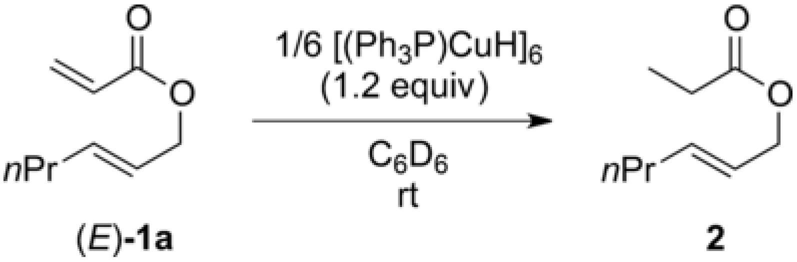
Abstract: An efficient reductive Claisen rearrangement, catalyzed by in situ generated copper hydride, and stoichiometric in diethoxymethylsilane, has been developed. Yields of up to 95% with good to excellent diastereoselectivities were observed in this reaction. Mechanistic studies showed that the stereospecific rearrangement proceeded via a chair transition state of (*E)*-silyl ketene acetals as intermediates, and not via the copper enolates.

The Ireland Claisen rearrangement[1] is a synthetically useful reaction, as it transforms an easily accessed ester C-O bond into a more valuable C-C bond, with the concomitant formation of up to two new stereogenic centers. Being a variant of the conventional thermal Claisen rearrangement,[2] it requires much lower operational temperatures. However, one limitation is the need to use strong bases in the generation of ester enolates, prohibiting its application in the context of base-sensitive substrates. Alternative conditions have thus been developed (Scheme 1), including Corey's borylation protocol.[3] Conjugate addition processes also furnished the enolate derivatives for the rearrangement.[4] In this connection, Morken's group reported a rhodium hydride-catalyzed reductive Claisen rearrangement variant,[5] in which silyl ketene acetals were generated by conjugate reduction of α,β-unsaturated allylic esters. Good yields and diastereoselectivities were observed, and base-sensitive functional groups were tolerated. However, the requirements of both the expensive metal and ligand,[6] and the highly moisture sensitive reductant Cl_2MeSiH, limit its wide application as a practical alternative to the traditional Claisen protocol. In contrast, copper hydrides are relatively non-basic species that are known to induce the conjugate reduction of Michael acceptors,[7] and are much more economical compared with rhodium. They have previously been utilized to mediate and catalyze reductive aldol reactions[8] and Michael additions[9], hydrostannation[10] and hydroboration.[11]. Therefore, the reductive Claisen rearrangement mediated by copper hydrides was investigated.



Scheme 1. Variants of the Ireland-Claisen rearrangement. (LICA= lithium isopropylcyclohexylamide)

The treatment of (*E*)-hex-2-enyl acrylate ((*E*)-**1a**) with a stoichiometric amount of Stryker's reagent, ie. [$(Ph_3P)CuH]_6$, resulted in simple reduction accompanied by side reactions, but notably, *no* Claisen rearrangement product was observed (Scheme 2). However, the reduction catalyzed by Stryker's reagent or copper hydride generated *in situ*, with pinacolborane (PinBH) as thestoichiometric reductant, continued onto a productive Claisen rearrangement in good yield (Table 1, entries 1-2). Similarly, the use of other reactive silanes also promoted the reductive Claisen rearrangement in modest yields (Table 1, entries 3-6). This indicated that the Claisen rearrangement did not proceed from the copper enolate obtained upon conjugate reduction, but via the enolborate or enolsilane intermediates obtained upon metathesis.



Scheme 2. NMR experiment - attempted reductive Claisen rearrangement with[$(Ph_3P)CuH]_6$

Table 1. Screening of reaction conditions.

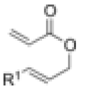
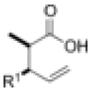
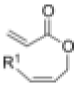
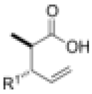
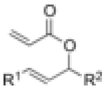
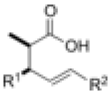
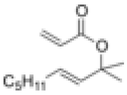
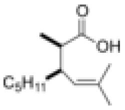
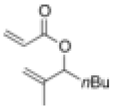
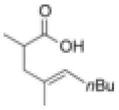
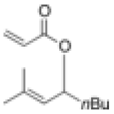
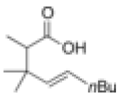
Entry	Conc.	Ligand[b]	Reductant	Yield (*anti:syn*)
1[a]	1.0 M	PPh_3	PinBH	76 % (1.6 : 1)
2[b]	0.5 M	-	PinBH	85 % (1 : 1.3)
3[a]	1.0 M	PPh_3	$PhSiH_3$	66 % (1.2 : 1)
4[a]	1.0 M	PPh_3	Ph_2SiH_2	51 % (1 : 1.5)
5[a]	1.0 M	PPh_3	$(EtO)_3SiH$	33 % (5 : 1)
6[a]	1.0 M	PPh_3	$(EtO)_2MeSiH$	18 % (6 : 1)
7[a]	1.6 M	PPh_3	$(EtO)_2MeSiH$	92 % (8 : 1)
8[a]	1.6 M	Ph_2PMe	$(EtO)_2MeSiH$	90 % (8 : 1)
9[c]	1.6 M	$P(OMe)_3$	$(EtO)_2MeSiH$	90 % (11 : 1)
10[c]	1.6 M	$P(OEt)_3$	$(EtO)_2MeSiH$	92 % (11 : 1)
11[c]	1.6 M	$P(OPh)_3$	$(EtO)_2MeSiH$	trace
12[c]	1.6 M	$P(O^iPr)_3$	$(EtO)_2MeSiH$	trace
13[d]	1.6 M	$P(OEt)_3$	$(EtO)_2MeSiH$	78 % (10 : 1)
14[e]	1.6 M	$P(OEt)_3$	$(EtO)_2MeSiH$	86 % (12 : 1)

[a] $Cu(OAc)_2.H_2O$ (5 mol %), ligand (10 mol %). [b] $[(Ph_3P)CuH]_6$ (5 mol %) [c] $Cu(OAc)_2$ (3.3 mol %), ligand (6.6 mol %), slow addition of substrate. [d] $Cu(OAc)_2.H_2O$ (3.3 mol %), ligand (6.6 mol %), slow addition of substrate. [e] $Cu(OAc)_2$ (3.3 mol %), ligand (6.6 mol %), slow addition of substrate, at 0 °C

Although PinBH facilitated a rapid reductive rearrangement in a good overall yield, the dr was low (Table 1, entries 1-2).[12] Phenylsilanes also promoted the reaction with low diastereoselectivities (Table 1, entries 3-4). On the other hand, the use of $(EtO)_2MeSiH$ (DEMS) facilitated a more diastereoselective reductive rearrangement for *anti*-**3a**, but the yield was disappointingly low (Table 1, entry 6). Surmising that the poor yield resulted from a lower turnover rate in the metathesis with $(EtO)_2MeSiH$, which would allow the unsequestered copper enolate intermediate to engage in side reactions, the reductant concentration was increased and maximized by adding (*E*)**-1a** slowly to the reaction mixture. Using this inverse addition protocol, the yield was dramatically improved (Table 1, entry 6 vs 7). Under these conditions, the copper catalyst loading could be decreased to 3 mol % without any detrimental effects. A screening of ligands showed that sterically unhindered phosphites such as $P(OEt)_3$ and $P(OMe)_3$ were the optimal ligands, providing the highest yields and diastereoselectivity for *anti*-**3a** (Table 1, entries 9 - 10), while bulkier phosphites (e.g. $P(OPh)_3$ and $P(O\textit{i}Pr)_3$) failed to facilitate the regeneration of copper hydride and arrested the catalytic cycle (Table 1, entries 11 - 12).

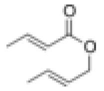
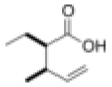
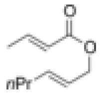
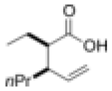
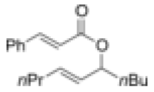
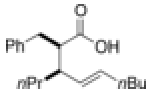
Toluene was found to be the best solvent. THF and benzene could also be used, but *anti*-**3a** was obtained with a slight decrease in dr (10:1, see SI). Small amounts of moisture is tolerated in the reaction but results in lower yields of rearrangement product (Table 1, entry 10 vs 13).[13] Decreasing the reaction temperature to 0 °C led to lower yields with only a marginal increase in dr (Table 1, entry 14). Having surveyed the reaction conditions, the scope of the copper-catalyzed reductive Claisen rearrangement was investigated. The reaction proceeded smoothly for all allylic acrylate substrates (Table 2). The reductive rearrangement reactions of the corresponding crotonate and cinnamate substrates were less efficient (Table 3). Substitution at all positions (C1, C4, C5, C6) were tolerated. A higher diastereoselectivity was observed in the reactions of substrates with bulky substituents at C4 (Table 2, entry 1 vs 9, 7 vs 8). Those substrates with a bulky R^1 reacted with further even higher diastereoselectivity (Table 2, entry 9 vs 10; Table 3, entry 1 vs 2). Notably, *anti*-**3d** could be obtained from the reductive Claisen rearrangement of **1d** (Table 2, entry 4), a product that would be challenging to obtain chemoselectively by a typical Ireland Claisen rearrangement approach. *(E)*- and (*Z)*-substrates (C5-C6 geometry) provided complementary diastereoselectivities (Table 2, entry 1 vs 5, 2 vs 6), with (*Z)*- substrates undergoing the rearrangement at a much slower rate (3 days vs 2 hours). The reaction can be conducted at lower substrate concentrations in good yields, provided that the other reagents are scaled up correspondingly, that is, by maintaining a high copper hydride concentration for fast reduction of substrates and a high silane concentration for fast trapping of copper enolates. In fact, this is necessary for the reductive rearrangement of substrates which are reduced slowly and are therefore particularly prone to intermolecular reactions (Table 3, entry 3), or when sensitive functional groups are present (e.g. OAc, Table 2, entry 4).

Table 2. Substrate scope.[a]

Entry	**Substrate (1)**	**Major product (3)**	**Yield [%] (*anti*/*syn*)[b]**
			
1[c]	(*E*)-**1 a**, R^1=*n*Pr	*anti*-**3 a**	92 (11:1)
2[d]	(*E*)-**1 b**, R^1=CH_2OTBS	*anti*-**3 b**	84 (10:1)
3	**1 c**, R^1=3,4,5-(OMe)3-Ph	*anti*-**3 c**	70 (>20:1)
4[e]	**1 d**, R^1=CH_2OAc	*anti*-**3 d**	76 (9:1)
			
5[c]	(*Z*)-**1 a**, R^1=*n*Pr	*syn*-**3 a**	81 (1:10)
6[f]	(*Z*)-**1 a**, R^1=CH_2OTBS	*syn*-**3 b**	84 (1:11)
			
7	**1 e**, R^1=Ph, R^2=*n*Bu	*anti*-**3 e**[g]	87 (22:1)[g]
8	**1 f**, R^1=Ph, R^2=Me	*anti*-**3 f**[g]	95 (17:1)[g]
9	**1 g**, R^1=*n*Pr, R^2=Cy	*anti*-**3 g**[g]	91 (29:1)[g]
10[h]	**1 e**, R^1=Me, R^2=Cy	*anti*-**3 h**[g]	90 (18:1)[g]
			
11[d]	**1 i**	*anti*-**3 i**	90 (7:1)
			
12	**1 j**	**3 j**[g]	89
			
13	**1 k**	**3 k**[g]	86

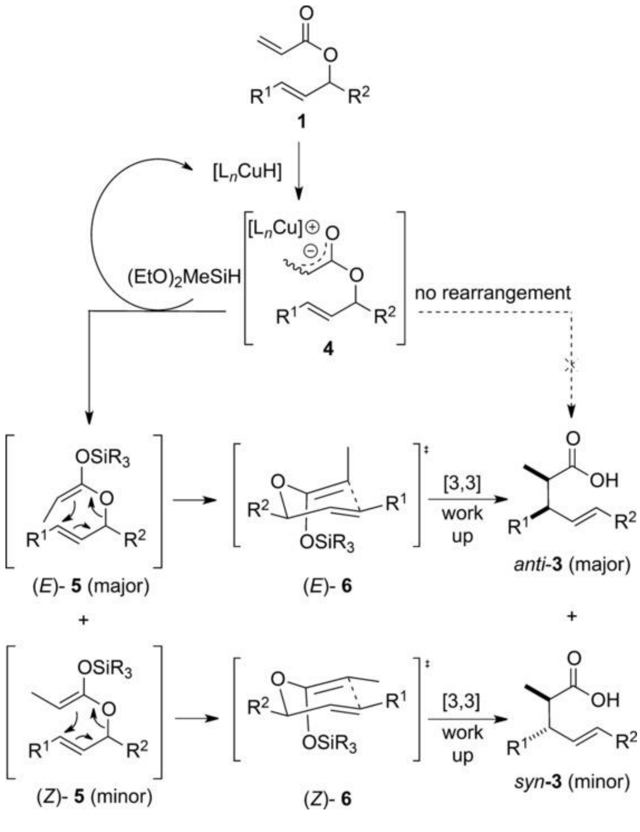
Typical conditions: 3.3 mol % $Cu(OAc)_2$, 6.6 mol % $P(OEt)_3$, 1.5 equiv. $(EtO)_2MeSiH$, toluene, rt, 2 h - 3 days. Yields are isolated product yields. [a] Determined by NMR integration. [b] Relative stereochemistry confirmed by comparison to literature. [c] Relative stereochemistry confirmed by conversion to γ-lactones. [d] 20 mol % $Cu(OAc)_2$, 40 mol % $P(OEt)_3$, 9 equiv. $(EtO)_2MeSiH$, 0.26 M. [e] Relative stereochemistry confirmed by comparison to the other diastereomer. [f] *E:Z* >20:1 (only one isomer observed) [g] Relative stereochemistry confirmed by X-ray crystallography.[14

Table 3. Substrate scope.[a]

Entry	**Substrate (1)**	**Major product (3)**	**Yield [%] (*anti*/*syn*)[b]**
1[c]			68 (5.4:1)
2			74 (9:1)
3[d]			36 (25:1)[e]

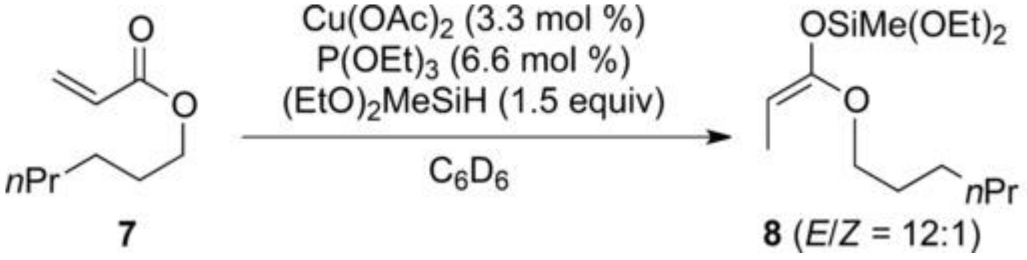
Typical conditions: 3.3 mol % $Cu(OAc)_2$, 6.6 mol % $P(OEt)_3$, 1.5 equiv. $(EtO)_2MeSiH$, toluene, rt, 9 h - 3 days. Yields are isolated product yields. [a] Determined by NMR integration. [b] Relative stereochemistry confirmed by comparison to literature. [c] 20 mol % $Cu(OAc)_2$, 40 mol % $P(OEt)_3$, 4.5 equiv. $(EtO)_2MeSiH$, 0.53 M. [d] *E : Z > 20 : 1* (only one isomer observed)

Mechanistically (Scheme 3), the reductive Claisen rearrangement did not proceed from the copper enolate **4**, but from the corresponding enolsilane or enolborate. This was inferred from the experiment in Scheme 1. This precluded the possibility to use chiral copper complexes to induce an enantioselective Claisen rearrangement. Other metal enolates are well-precedented to undergo Claisen rearrangements.[2b] The fact that no rearrangement followed the copper-catalyzed conjugate reduction could be experimental evidence supporting suggestions that the copper enolate **4** is predominantly a C-bound enolate.[15]



Scheme 3. Proposed mechanism of copper hydride-catalyzed reductive Claisen rearrangement

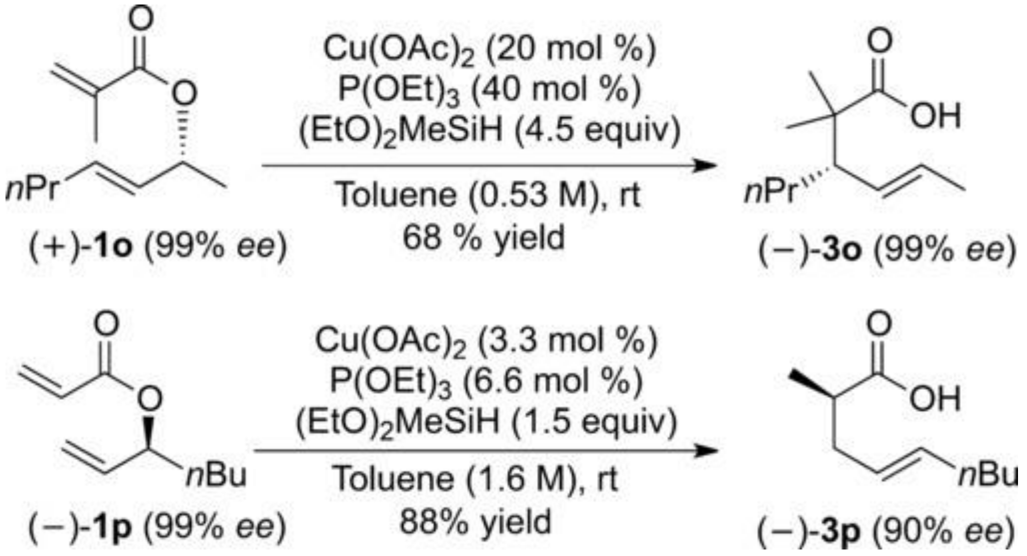
The diastereoselectivity observed is consistent with copper hydride reduction forming selectively (*E)*-silyl ketene acetals (*E*)-**5**, that undergo the Claisen rearrangement via a chair transition state (*E*)-**6**, resulting in *anti*-**3** (Scheme 3). Indeed, the reduction of acrylate **7**, which cannot proceed to rearrangement, yielded predominantly (*E)*-**8** as observed by NMR (Scheme 4).



Scheme 4. NMR experiment - selective formation of (*E)*-**8**

The stereospecificity of the rearrangement with respect to C5- C6 double bond geometry[1b] is consistent with the chair transition state model proposed by Ireland.[1b] It also explains the less efficient reductive rearrangements of **1l**-**1n**, because the β–substituents would occupy axial positions in the chair transition state (*E)*-**6** (Scheme 3).

Starting from optically enriched acrylate **1o,** perfect chirality transfer[16] from C4 to C6 yielded **3o** (Scheme 5). The partial loss in chirality in the reductive rearrangement of **1p** can be explained by the fact that silyl ketene acetals (*E)*-**5** and (*Z)*-**5** rearrange to give opposite enantiomers respectively (Scheme 3). In this case, silyl ketene acetals of an *E* : *Z* ratio of 19 : 1 can be inferred from the 9% loss in enantiomeric excess.



Scheme 5. Chirality transfer in reductive Claisen rearrangement[17]

In conclusion, a copper hydride catalyzed reductive Claisen rearrangement has been developed. Using a relatively inexpensive metal and ligand combination, good yields and diastereoselectivity were obtained in this overall reaction. Mechanistically, the rearrangement has been shown to proceed through the (*E)*-silyl ketene acetals, and not the copper enolates, via a chair transition state. Since the substrates are also obtained readily from unsaturated acids, overall, this method constitutes a practical alternative version of the Claisen rearrangement that shows a useful chemoselectivity compared with the traditional base-induced Ireland Claisen protocol.

Experimental Section

For the highest yields, $Cu(OAc)_2$ was handled inside the glovebox. $Cu(OAc)_2$ (6.0 mg, 0.033 mmol, 3.3 mol %) was weighed into an oven- dried conical vial with a magnetic stir bar, then sealed with a septum and removed from the glovebox. Under argon, dry and degassed toluene (0.63 mL) was added, followed by the addition of $P(OEt)_3$ (11.5 μL, 0.067mmol, 6.7 mol %). The reaction was stirred vigorously for 15 minutes (Note: vigorous stirring is essential for maximum dissolution of $Cu(OAc)_2$ in toluene). $(EtO)_2MeSiH$ (0.24 mL, 1.5 mmol, 1.5 equiv.) was added and stirred for 3 h at room temperature. Typically, the reaction becomes red- orange within 1h. The substrate (1.0 mmol) was then added slowly dropwise over 10-15 minutes. The red-orange color of the reaction is maintained throughout the addition. The reaction mixture was further stirred at room temperature until complete consumption of starting materials as judged by TLC. The reaction solution was then directly loaded onto a silica gel column, for flash column chromatography to obtain the purified products.

Acknowledgements

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Keywords: copper • hydride • Claisen rearrangement • reduction • silane

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[12] The use of *anti* and *syn* labels follows the typical convention used in ref. 5, in which the relative stereochemistry of the two substituents is defined for the carboxylic acid drawn as a straight chain.

[13] For additional experiments of screening of reaction conditions, see Supplementary Information.

[14] Full crystallographic data for *anti*-**3h** (CCDC 1439980) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data%5Frequest/cif

[15] This could evidence for the intermediacy of a C-copper enolate instead of an O-copper enolate, see:

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[17] The absolute stereochemistry of (–)-**3o** was assumed from chair transition state model; that of (–)-**3p** was deduced from hydrogenation to generate (*R*)-2-methylnonanoic acid.