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Conjugate Addition/Ireland−Claisen Rearrangements of Allyl Fumarates: Simple Access to Terminally Differentiated Succinates

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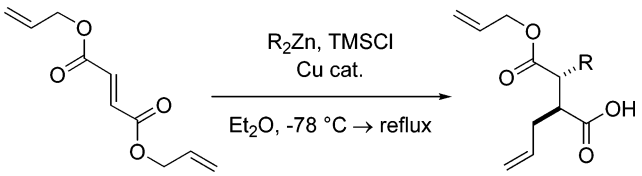
Received October 19, 2007

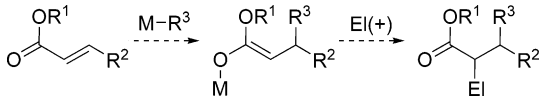


The conjugate addition of dialkylzinc reagents to allyl fumarates with subsequent Ireland−Claisen rearrangement has been accomplished yielding substituted unsymmetrical succinic acid derivatives. This one-pot reaction creates two new carbon−carbon bonds at contiguous stereogenic centers. The reaction proceeds for several alkylzinc reagents and substituted allyl fumarates. The products contain distinguishable functional handles for further manipulation.

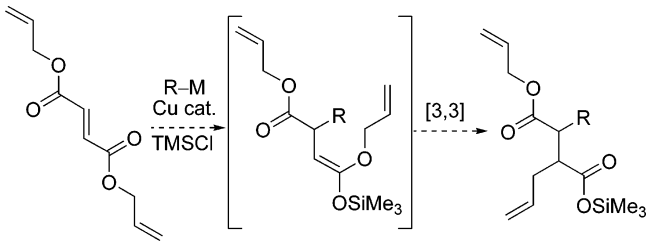
The conjugate addition of nonstabilized organometallic nucleophiles to α,*β*-unsaturated carbonyls is a staple of organic synthesis, but the fumarate and maleate electrophile subclass in this reaction family has received scant attention relative to simple enones and enoates. The comparative lack of research activity is surprising since maleic and fumaric acid derivatives represent cheap progenitors to functionalized succinic acids. Notable advances in this area have been reported. Ibuka and co-workers disclosed organocopper(I)−Lewis acid additions to fumarate esters that afforded good yields of the addition products; however, olefin reduction was a competing reaction pathway.[1] Hayashi and co-workers have reported enantioselective rhodium-catalyzed 1,4-additions of arylboronic acids to fumarates and maleates.[2] While these examples provide useful conjugate adducts, a nonobvious feature of the reported additions is that the carbonyls in the products are still functionally equivalent and therefore challenging to distinguish. In this paper, we describe the conjugate addition of dialkylzinc reagents to diallyl fumarates with subsequent Ireland−Claisen rearrangement to give unsymmetrical succinate products. A defining characteristic of the title reaction is chemodifferentiation of the two carbonyls that can be exploited in further selective manipulations.

Multicomponent couplings initiated by conjugate addition and terminated by electrophilic trapping of the resulting enolate are classic complexity-building reactions that exploit that latent nucleophilic character of the α-carbon in Michael acceptors (Scheme 1).[3] Conjugate addition/[3,3]-rearrangement reactions represent an important subcategory of these tandem processes.[4] We envisioned that by using an allyl fumarate as the conjugate acceptor with an organometallic nucleophile, the metal enolate or derived silyl ketene acetal generated in situ would undergo a subsequent ester enolate Claisen rearrangement (Scheme 2).[5] In accord with precedent, the use of a chlorotrialkylsilane was projected to both accelerate the conjugate addition and generate the requisite silyl ketene acetal.[6,7]

SCHEME 1. General Three-Component Coupling with Enoates



SCHEME 2. Proposed Conjugate Addition/[3,3]-Rearrangement



Organometallic nucleophiles for conjugate addition to diallylfumarates[8] were evaluated. For the purpose of the initial screen, we examined only the 1,4-addition. The two catalysts utilized were the commercially available CuBr·SMe_2 and easily synthesized bis(*N-tert*-butylsalicylideneaminato)copper(II),[9] hereafter referred to as Cu(N^tBu·sal)$_2$.

The Cu(N^tBu·sal)$_2$-catalyzed addition of ethylmagnesium bromide led to the desired 1,4-addition product along with products derived from 1,2-addition and S_N2' displacement (Table 1, entry 1). The conjugate addition of ethylmagnesium bromide also proceeds in the absence of copper (entry 2). An alternative organometallic reagent, diethylzinc, is considerably less reactive in THF (entry 3), but simply switching solvents to diethyl ether provides clean conjugate addition in 90 min (entries 4 and 5).

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(8) See the Supporting Information for the synthesis procedure.

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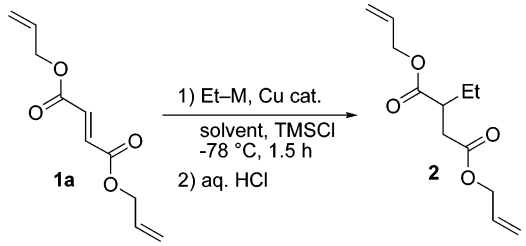
10.1021/jo701778k CCC: $40.75
Published on Web 01/23/2008

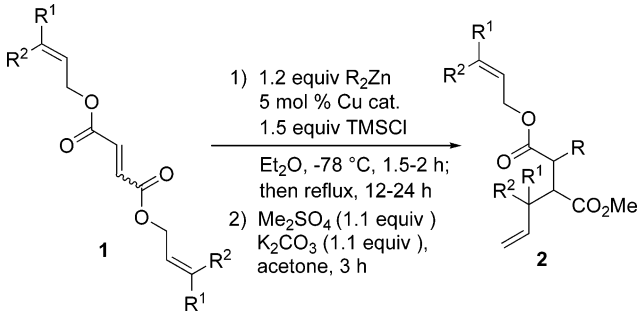
TABLE 1. Initial Results of Conjugate Addition to Diallyl Fumarate



entry	EtM	solvent	catalyst	results[a]
1	EtMgBr	THF	$Cu(N^tBu\cdot sal)_2$	mix of products[b]
2	EtMgBr	THF	None	85% conv
3	Et_2Zn	THF	$Cu(N^tBu\cdot sal)_2$	12% conv
4	Et_2Zn	Et_2O	$Cu(N^tBu\cdot sal)_2$	100% conv
5	Et_2Zn	Et_2O	CuBr·DMS	100% conv
6[c]	Et_2Zn	Et_2O	$Cu(N^tBu\cdot sal)_2$	74% conv
7	Et_2Zn	Et_2O	none	80% conv
8[c]	Et_2Zn	Et_2O	none	60% conv

[a] Conversion determined by ^1H NMR spectroscopy. [b] Undetermined mixture of 1,4-addition, 1,2-addition, and S_N2'. [c] Reaction conducted without TMSCl.

TABLE 2. Scope of Tandem Michael Addition/Ireland−Claisen Rearrangement



entry	R_2Zn	substrate	product	yield (%) (dr)[a]
1	Et_2Zn	(*E*)-**1a** (R^1, R^2 = H)	**2a**	83 (9:1)
2	Et_2Zn	(*Z*)-**1a** (R^1, R^2 = H)	**2a**	74 (6.5:1)
3	Et_2Zn	(*E*)-**1b** (R^1, R^2 = Me)	**2b**	68 (7.5:1)
4	$^iPr_2Zn$	(*E*)-**1a** (R^1, R^2 = H)	**2c**	70 (4.9:1)
5	Bu_2Zn[b]	(*E*)-**1a** (R^1, R^2 = H)	**2d**	88 (4.5:1)
6	Bu_2Zn[b]	(*E*)-**1a** (R^1, R^2 = Me)	**2e**	63 (2:1)
7	Et_2Zn	(*E*)-**1c** (R^1 = Me, R^2 = H)	**2f**	75 (mix)
8	Et_2Zn	(*E*)-**1d** (R^1 = H, R^2 = Pr)	**2g**	78 (mix)

[a] Yield of isolated products purified by column chromatography. [b] 1.5 equiv of Bu_2Zn (generated from 3.0 equiv of BuLi and 1.5 equiv of $ZnCl_2$ in Et_2O), 4.0 equiv of TMSCl.

The desired addition proceeds in the absence of TMSCl and copper additives (entries 6−8), although with decreased efficiency. The observation of uncatalyzed addition using Et_2Zn, even at low temperature, dramatically highlights the difference in reactivity between fumarates and simple enoates. The identity of the copper source was inconsequential to the progress of the reaction. Upon heating of the reaction mixture, the presumed silylketene acetal intermediate underwent Ireland−Claisen rearrangement. The carboxylic acid product was esterified with dimethyl sulfate and potassium carbonate in acetone for ease of characterization. With the optimized conditions identified, the scope of the reaction was explored (Table 2).

The addition of diethylzinc (1.0 M in diethyl ether) to diallyl fumarate (entry 1) or diallyl maleate (entry 2) and subsequent rearrangement provides the disubstituted unsymmetrical succinate product in good yield and diastereocontrol. Diprenyl fumarate is also an effective reaction partner (entry 3), with S_N2' displacement as a competitive process that slightly decreases the yield. The diastereoselectivity is eroded when a bulkier nucleophile, diisopropylzinc (1.0 M in toluene), is used (entry 4).

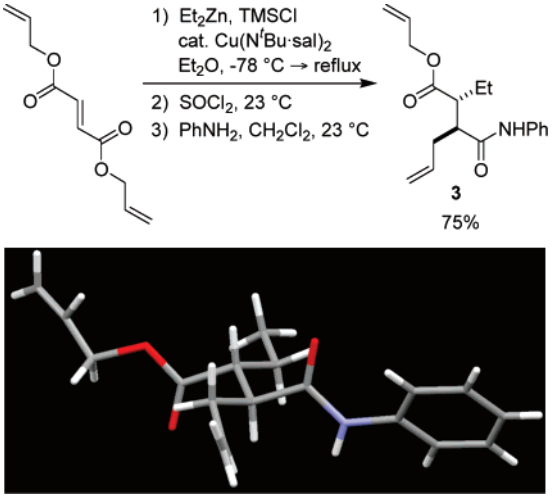


FIGURE 1. X-ray structure of amide **3**.

Other diorganozinc reagents were prepared *via* transmetalation. By using *n*-butyllithium and $ZnCl_2$ to generate $Bu_2Zn\cdot(LiCl)_2$ in situ, the desired addition and subsequent rearrangement was accomplished. The addition of $Bu_2Zn\cdot(LiCl)_2$ to both diallyl and diprenyl fumarates proceeded in good yield, although with decreased diastereoselectivity (entries 5 and 6). The reagent $Bu_2Zn\cdot(MgX_2)_2$ gave rise to the desired 1,4-addition, but with little or no rearrangement observed. It is conceivable that the magnesium salts inhibit the enolate silylation that is apparently required for the [3,3]-rearrangement.

The addition of Et_2Zn to either a cis- (entry 8) or trans-substituted (entry 7) allyl fumarate proceeds in good yield but gives an intractable mixture of diastereomers.

The monocarboxylic acid derived from addition of diethylzinc to diallyl fumarate (**1a**) was transformed in two steps to the crystalline secondary amide **3**. Its relative stereostructure was ascertained via X-ray crystallography.[10] The structure found in Figure 1 reveals the anti disposition of the ethyl and allyl moieties on the succinate backbone. A stereochemical model consistent with this observation supposes that addition to the favored s-trans conformation of the enoate occurs to give an (*E*)-enolate intermediate.[11] In a relevant study, Blanco and co-workers reported that conjugate addition to the s-trans conformation of an α,β-unsaturated enoate led to the *E*-silylketene acetal geometry upon trapping with chlorotrimethylsilane.[7d] A transition structure for the sigmatropic rearrangement that minimizes allylic strain and involves approach of the allyl moiety syn to the ester group has been previously invoked by Martin and co-workers in their study of Ireland−Claisen rearrangements of substituted succinates (Scheme 3).[12]

The desymmetrized succinate products are useful due to the presence of several distinguishable functional handles that allow

(10) CCDC 635154 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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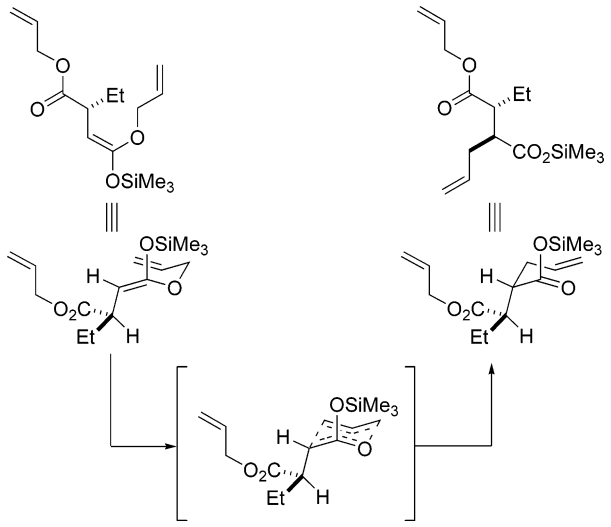
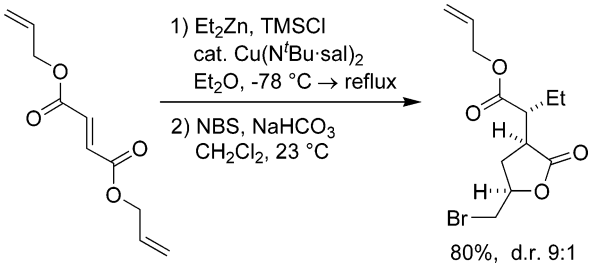
SCHEME 3. Proposed Transition State for Ireland−Claisen Rearrangement



SCHEME 4. Site-Selective Bromolactonization

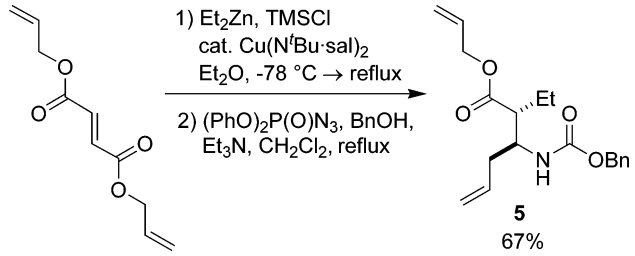


for further synthetic manipulation. Subjecting the carboxylic acid intermediate to *N*-bromosuccinimide[13] in the presence of $NaHCO_3$ gave efficient bromolactonization yielding the γ-lactone (Scheme 4) in 80% yield and 9:1 diastereoselection. The diastereomers result from the initial addition/sigmatropic rearrangement, indicating that the cyclization proceeds with complete diastereoselectivity.[14]

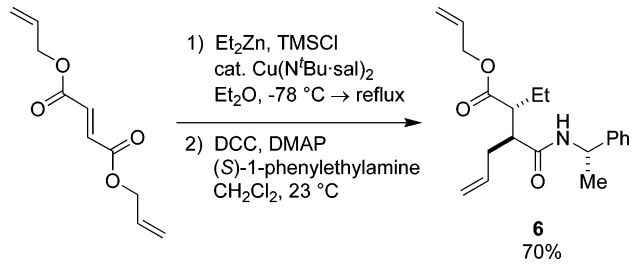
Alternatively, the carboxylic acid can be employed in a Curtius rearrangement to furnish a β-amino ester with diphenylphosphoryl azide, benzyl alcohol, and triethylamine (Scheme 5).[15] No purification of the intermediate acid was performed for either the bromolactonization or Curtius rearrangement.

The amide formed with the racemic rearranged product and (*S*)-phenylethylamine using DCC[16] gives a secondary amide as

SCHEME 5. Curtius Rearrangement to a β-Amino Ester



SCHEME 6. DCC Coupling of Carboxylic Acid and Amine



a 1:1 mixture of diastereomers (Scheme 6). The diastereotopic methyl groups are clearly distinguishable by ^{1}H NMR spectroscopy (δ 0.87 vs 0.78, $CDCl_3$), which allows this simple derivative to be used for assaying enantioselective variants. Efforts to this end employing methods developed by Feringa[17] and others have provided no enantiomeric enrichment to date. The significant uncatalyzed background rate is almost certainly a complication in these efforts. To achieve an enantioselective variant, a substantially less reactive nucleophile will need to be incorporated into this tandem sequence to suppress the background addition of the achiral nucleophile.

In summary, we have developed a tandem conjugate addition/Ireland-Claisen rearrangment of dialkylzinc reagents and allyl fumarates in good to excellent yields giving substituted succinate products. The reaction renders the two carboxyl groups nonequivalent; consequently, the products can be selectively manipulated in subsequent synthetic operations.

Acknowledgment. Funding for this work was provided by the National Institutes of Health (National Institute of General Medical Sciences, GM068443). Research support from Eli Lilly, Amgen, and GSK is gratefully acknowledged. J.S.J. is an Alfred P. Sloan Fellow and a Camille Dreyfus Teacher−Scholar.

Supporting Information Available: Spectroscopic and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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