

Sc(OTf)₃-Catalyzed Conjugate Allylation
of Alkylidene Meldrum's Acids

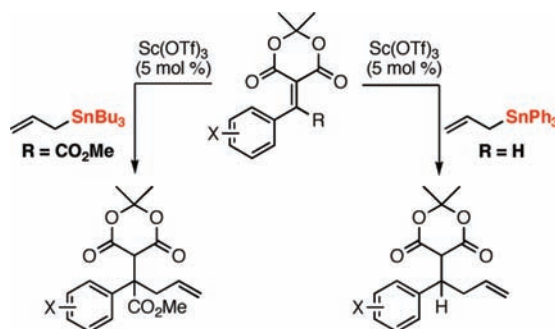
Aaron M. Dumas and Eric Fillion*

Department of Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

efillion@uwaterloo.ca

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ABSTRACT



Alkylidene Meldrum's acids are allylated in a conjugate fashion by allyltin nucleophiles under mild Sc(OTf)₃-catalyzed conditions. The addition is functional group tolerant and reactions with nonracemic alkylidenes are highly diastereoselective. Allylation of alkylidenes derived from α -ketoesters yield all-carbon quaternary stereocenters.

Nucleophilic addition of an allyl group is a fundamental C–C bond forming reaction. In particular, 1,2-addition of allyl nucleophiles to carbonyls has been studied extensively and a large selection of catalytic conditions for this process have been developed.¹ However, catalytic 1,4-conjugate allylation of α,β -unsaturated carbonyls is significantly less developed compared to other carbon nucleophiles, although methods involving stoichiometric amounts of Lewis acids² or nucleophilic activators³ are known.⁴ For example, in contrast to the plethora of catalytic enantioselective 1,2-allylations⁵ there are at present only two methods for catalytic enantioselective 1,4-allylation, as reported recently by Morken⁶ and Snapper.⁷

A major difficulty in investigating conjugate allylation is competing 1,2- vs 1,4-addition, which is often dependent on the combination of nucleophile and electrophile. In particular, conjugate allylation of enones and enals remains a challenging objective.^{8,9} Therefore, development of a general, catalytic conjugate allylation would be aided by the use of electrophiles for which 1,2-addition can be suppressed but are easily converted into a range of carbonyl derivatives.¹⁰ In this regard, recent work by Jarvo has shown that Pd-NHC complexes catalyze the addition of allylboranes to unsaturated *N*-acylpyrroles and alkylidene malononitriles in a

(1) Selected recent examples: (a) Barker, T. J.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 1047–1049. (b) Denmark, S. E.; Nguyen, S. T. *Org. Lett.* **2009**, *11*, 781–784. (c) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899. (d) Raunyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490. (e) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. For a general review on reactions of allyl metal reagents, see: (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.

(2) Initial discovery using allylsilanes: (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673–1675. Allylstannanes: (b) Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, *8*, 977–980.

(3) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. J. *Org. Chem.* **1986**, *51*, 1745–1753.

(4) Conjugate allylation of nitroalkenes: (a) Shen, K.-H.; Liu, J.-T.; Wu, Y.-R.; Yao, C.-F. *Synth. Commun.* **2007**, *37*, 3677–3687. (b) Kumar, H. M. S.; Reddy, B. V. S.; Reddy, P. T.; Yadav, J. B. *Tetrahedron Lett.* **1999**, *40*, 5387–5388. (c) Barboni, L.; Bartoli, G.; Marcantoni, E.; Petrini, M.; Dalpozzo, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2133–2138. (d) Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597–3603. (e) Uno, H.; Watanabe, N.; Fujiki, S.; Suzuki, H. *Synthesis* **1987**, 471–474.

(5) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2794.

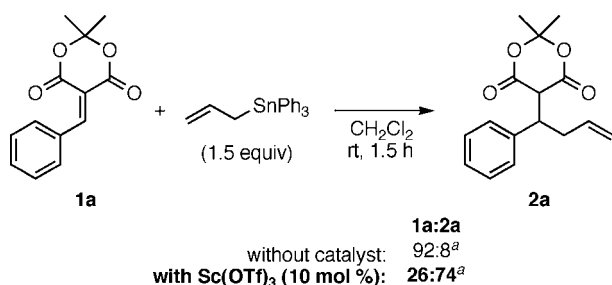
(6) (a) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983. (b) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214–2215.

(7) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049–5051.

catalyst-controlled, highly regioselective manner.¹¹ Herein we report that alkylidene Meldrum's acids are excellent acceptors for Sc(OTf)₃-catalyzed conjugate allylation under mild reaction conditions.¹² The use of alkylidene Meldrum's acids for conjugate allylation provides a number of advantages, owing to their ease of preparation,¹³ high electrophilicity,¹⁴ and the versatility of the Meldrum's acid group in subsequent transformations. Importantly, Meldrum's acid derivatives can be converted directly into both ketones¹⁵ and aldehydes,¹⁶ as well as carboxylic acids, esters, and amides.¹⁷

In order to minimize potential 1,2-addition and allow maximum functional group compatibility, a goal of the investigation was to use the least nucleophilic allylating agent possible.¹⁸ Initial attempts using benzylidene Meldrum's acid **1a** as electrophile and allyltrimethylsilane as nucleophile were unsuccessful. In the presence of a variety of Lewis acid catalysts no reaction occurred and the starting materials were unchanged. Increasing the nucleophilicity by switching to allyltriphenylstannane revealed a slow uncatalyzed reaction; addition of 10 mol % Sc(OTf)₃ resulted in a substantial increase in conversion (Scheme 1).

Scheme 1. Conjugate Allylation of **1a** with AllylSnPh₃^a



^a Ratio **1a:2a** determined by analysis of the ¹H NMR of the crude reaction mixture following acidic workup.¹⁹

Further optimization of reaction conditions allowed reduction of both the catalyst loading and the amount of allyl-SnPh₃. As shown in Table 1, standard reaction conditions involve 1.0 mmol of alkylidene Meldrum's acid, 1.3 mmol

of allylSnPh₃ and 5 mol % of Sc(OTf)₃; using **1a** as electrophile, **2a** was obtained in 85% yield after 21 h at room temperature (entry 1).

Table 1. Sc(OTf)₃-Catalyzed Allylation of Alkylidene Meldrum's Acids

entry	R	product	% yield ^a
1	C ₆ H ₅ (1a)	2a	85
2	4-MeC ₆ H ₄ (1b)	2b	87
3	4-(CN)C ₆ H ₄ (1c)	2c	91
4 ^b	4-(OMe)C ₆ H ₄ (1d)	2d	82
5 ^b	4-(NO ₂)C ₆ H ₄ (1e)	2e	83
6	4-ClC ₆ H ₄ (1f)	2f	85
7	2-FC ₆ H ₄ (1g)	2g	74
8	3-(OTIPS)C ₆ H ₄ (1h)	2h	80
9	2-naphthyl (1i)	2i	91
10 ^c	1-naphthyl (1j)	2j	88
11 ^d	2-thienyl (1k)	2k	86
12 ^c	3-(N-Ts)indolyl (1l)	2l	89
13 ^d	2-(N-Ts)pyrrolyl (1m)	2m	76
14	Me (1n)	2n	73
15	<i>i</i> -Pr (1o)	2o	83
16 ^d	<i>t</i> -Bu (1p)	2p	77

^a Isolated yield. ^b Reactions conditions: 1,2-dichloroethane, 50 °C, 21 h. ^c Sc(OTf)₃ (0.1 mmol) used. ^d Reaction ran for 36 h with 0.15 mmol Sc(OTf)₃.

The reaction is general across a range of substituted and functionalized benzylidene Meldrum's acids (Table 1, entries 1–8); in the case of **1d**, running the reaction at higher temperature allowed complete conversion of the less reactive electron-rich starting material (entry 4). Higher temperature was also useful for **1e**, which reacts slowly due to its low solubility at rt (entry 5). As an alternative to running reactions at higher temperature, increased catalyst loading and reaction

(8) For recent examples of 1,2-allylation of enals and enones using allyltin reagents, see: (a) Zhang, T.; Shi, M.; Zhao, M. *Tetrahedron* **2008**, *64*, 2412–2418. (b) Lingaiah, B. V.; Ezikiel, G.; Yakaiah, T.; Reddy, G. V.; Rao, P. S. *Tetrahedron Lett.* **2006**, *47*, 4315–4318. Enones: (c) Wooten, A. J.; Kim, J. G.; Walsh, P. J. *Org. Lett.* **2007**, *9*, 381–384. (d) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743–2745.

(9) Conjugate allylation of cinnamaldehyde with allyllithium in the presence of a bulky aluminum phenoxide reagent has been reported: Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1183–1185.

(10) Conjugate allylation of enones with catalytic indium and excess TMSCl: Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189–2193.

(11) (a) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743–4746. (b) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2009**, *65*, 3197–3201.

(12) Isolated examples of conjugate allylation in the presence of Lewis acids to alkylidene Meldrum's acids containing metallated dienes have been reported, see: (a) Wada, C. K.; Roush, W. R. *Tetrahedron Lett.* **1994**, *35*, 7351–7354. (b) Paley, R. S.; Estroff, L. A.; Gauguier, J.-M.; Hunt, D. K.; Newlin, R. C. *Org. Lett.* **2000**, *2*, 365–368. For an intramolecular example, see: (c) Tietze, L. F.; Ruther, M. *Chem. Ber.* **1990**, *123*, 1387–1395.

(13) Dumas, A. M.; Seed, A.; Zorzitto, A. K.; Fillion, E. *Tetrahedron Lett.* **2007**, *48*, 7072–7074.

(14) Alkylidene Meldrum's acids are significantly more electrophilic than the corresponding diethyl alkylidenemalonates, see: Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738–2745.

(15) For transformations into arylketones, see: (a) Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920–2923. (b) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327. (c) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653–4656.

(16) Frost, C. G.; Hartley, B. C. *Org. Lett.* **2007**, *9*, 4259–4261.

(17) For reviews on transformations of Meldrum's acid derivatives, see: (a) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789–811. (b) Chen, B. C. *Heterocycles* **1991**, *32*, 529–597. (c) Strozhev, M. F.; Lielbriedis, I. E.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1991**, 579–599. (d) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358.

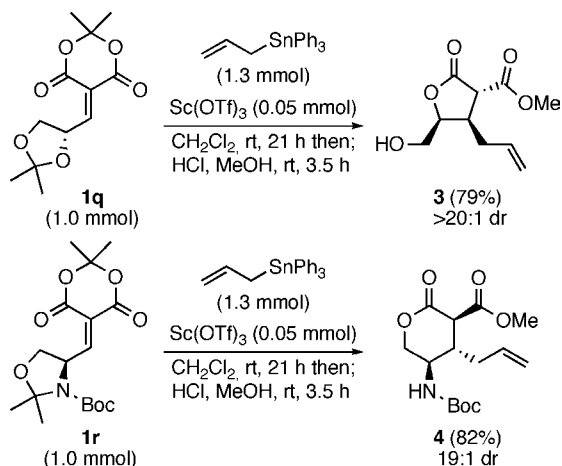
(18) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.

(19) The initial product formed by allylation is a triphenyltin enolate of Meldrum's acid that is protonated by acidic workup. See Supporting Information.

time can be used in the case of sterically hindered (entry 10) or electron-rich acceptors (entries 11–13). The reaction proceeds equally well for methyldene Meldrum's acids (entries 14–15), even those possessing a bulky *t*-Bu group (entry 16). Of note are successful reactions with substrates containing functional groups incompatible with Pd-catalyzed^{11a} (entries 6 and 7) or fluoride-activated (entry 8) conjugate allylation protocols.³

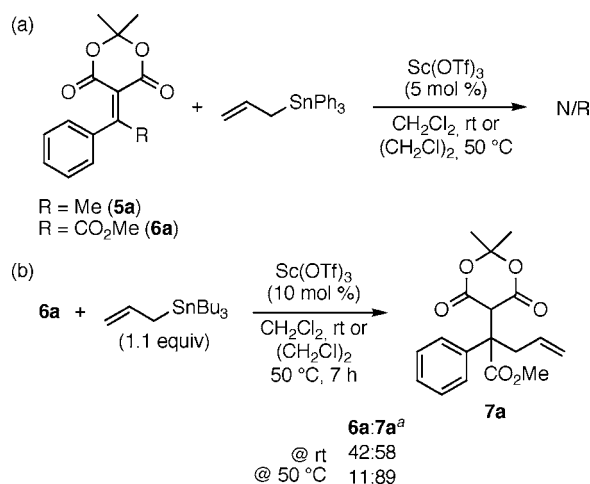
Conjugate allylation of chiral, nonracemic alkylidene Meldrum's acid **1q**²⁰ proceeded equally well at rt, and in high diastereoselectivity by analysis of the crude reaction mixture, however the allylated Meldrum's acid derivative proved unstable and could not be isolated cleanly.^{21,22} Therefore a one-pot procedure involving Sc(OTf)₃-catalyzed conjugate allylation followed by treatment with HCl in MeOH; which deprotected the acetonide and promoted lactonization/esterification to furnish **3** with a dr > 20:1 (Scheme 2). Similar treatment of **1r**, derived from Garner's aldehyde, gave the δ -lactone **4** in 19:1 dr.²³

Scheme 2. Diastereoselective Conjugate Allylation/Lactonization



The above reactions formed tertiary centers through allylation of alkylidene Meldrum's acids derived from aldehydes. A more difficult transformation is addition to tetrasubstituted alkylidenes to form all-carbon quaternary stereocenters. Precedent from our group has shown that alkylidenes of type **5** and **6** are excellent substrates to access this challenging motif.²⁴ Subjecting **5a** and **6a** to allylSnPh₃ under conditions optimized for alkylidenes **1** resulted in no conversion (Scheme 3a). Increasing the nucleophilicity of

Scheme 3. Conjugate Allylation to Generate All-Carbon Quaternary Centers^a

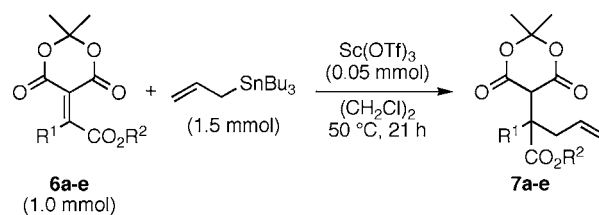


^a Ratio **4a:5a** determined by analysis of the ¹H NMR of the crude reaction mixture following acidic workup.

the allylating agent by using allylSnBu₃, a Sc(OTf)₃-catalyzed addition to **6a** was observed. The conversion could be increased by performing the reactions at 50 °C in 1,2-dichloroethane (Scheme 3b). No addition occurred to the less reactive **5a** under either of these conditions.

By increasing the amount of allylSnBu₃ and the reaction time, catalyst loading was reduced to 5 mol %; on a 1 mmol scale reaction of **6a** gave allylated product **7a** in 81% yield (Table 2, entry 1). The reaction was tolerant of electron-

Table 2. Conjugate Allylation of Tetrasubstituted Alkylidene Meldrum's Acids **5**



entry	alkylidene	R ¹	R ²	product (% yield ^a)
1	6a	Ph	Me	7a (81)
2	6b	4-BrC ₆ H ₄	Me	7b (76)
3	6c	4-(<i>t</i> -Bu)C ₆ H ₄	Me	7c (82)
4	6d	2-naphthyl	Me	7d (85)
5	6e	Ph	allyl	7e (78)

^a Isolated yield.

donating and electron-withdrawing groups (entries 2 and 3, respectively), increased steric hindrance (entry 4), and

(23) Relative stereochemistry was determined by analysis of coupling constants and proceeds with the same facial selectivity as the addition of indole (ref 22).

(20) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964–4967.

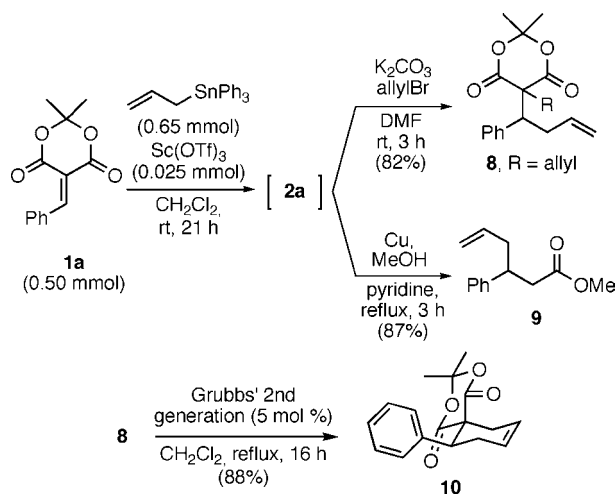
(21) For other examples of diastereoselective conjugate allylation not found in refs 2 and 3, see: (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 8071–8074. (b) Sato, M.; Aoyagi, S.; Yago, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 9063–9066. (c) Pan, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469–1472.

(22) For conjugate addition of indole to **1q** and **1r** formed in situ, see: (a) Boisbrun, M.; Kovács-Kulyassa, Á.; Jeannin, L.; Sapi, J.; Toupet, L.; Laronze, J.-Y. *Tetrahedron Lett.* **2000**, *41*, 9771–9775. (b) Dardennes, E.; Kovács-Kulyassa, Á.; Boisbrun, M.; Petermann, C.; Laronze, J.-Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1329–1339.

different esters (entry 5). No products of 1,2-allylation of either the Meldrum's acid or ester groups were detected in the ^1H NMR of the crude reaction mixture.

As mentioned above, the presence of Meldrum's acid in the allylated products **2** is useful as it provides a highly reactive handle for further transformations. As shown in Scheme 4, the crude reaction mixture following allylation

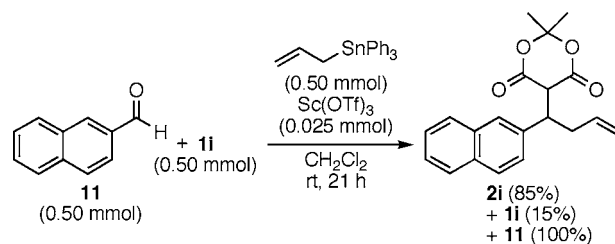
Scheme 4. Transformations of Allylated Meldrum's Acid **2a**



of **1a** was treated with weak base and allyl bromide to provide 5,5-disubstituted Meldrum's acid derivative **8** in 82% yield over two steps. Similarly crude **2a** was converted into methyl ester **9** by Cu-catalyzed esterification/decarboxylation.^{24a} The transformed products can themselves be reacted further, as shown by the ring-closing metathesis of **8** to give cyclohexene **10**.²⁵

In terms of chemoselectivity, the reactivity of alkylidene Meldrum's acids **1** is exceptional. Of note, a competition experiment between 2-naphthaldehyde (**11**) and the corresponding alkylidene **1i** demonstrated complete selectivity for formation of **2i** over 1,2-allylation (Scheme 5). Since a

Scheme 5. Chemoselective Allylation of **1i**^a



^a Yields in brackets determined by ^1H NMR integrations versus an internal standard of mesitylene. See Supporting Information.

control reaction between **11** and allylSnPh₃ with catalytic Sc(OTf)₃ did provide homoallylic alcohol,²⁶ it seems likely that the selectivity arises primarily from the enhanced electrophilicity of the alkylidenes.

Alkylidene Meldrum's acids have been shown to be excellent acceptors for conjugate allylation. The high reactivity of the alkylidenes combined with the versatility of the Meldrum's acid moiety makes this an attractive method for accessing a variety of δ,ϵ -unsaturated carbonyl compounds, including those bearing the challenging all-carbon quaternary center. Highly diastereoselective additions to nonracemic alkylidenes affords chiral lactones with synthetically useful handles for further transformations. Efforts to develop an enantioselective version of this method are underway.

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Supporting Information Available: Experimental details and characterization of all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) See Supporting Information for details.

(24) (a) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804. (b) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775.

(25) Similar products have been obtained by the reaction of alkylidene Meldrum's acids with butadiene sulfone: Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899–9902.