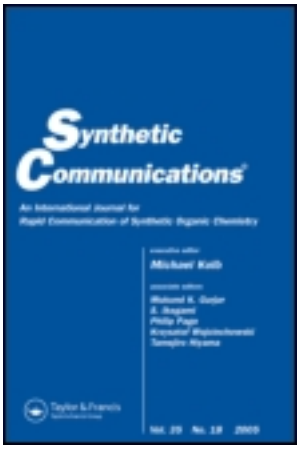


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Mild, Rapid, and Inexpensive Microwave-Assisted Synthesis of Allylic and Propargylic Esters

Monica A. Gill [a] & Jeffrey M. Manthorpe [a]

[a] Department of Chemistry, Carleton University, Ottawa, Ontario, Canada

Accepted author version posted online: 08 Aug 2012.Version of record first published: 05 Mar 2013.

To cite this article: Monica A. Gill & Jeffrey M. Manthorpe (2013): Mild, Rapid, and Inexpensive Microwave-Assisted Synthesis of Allylic and Propargylic Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:10, 1460-1468

To link to this article: http://dx.doi.org/10.1080/00397911.2011.640970

Synthetic Communications®, 43: 1460–1468, 2013

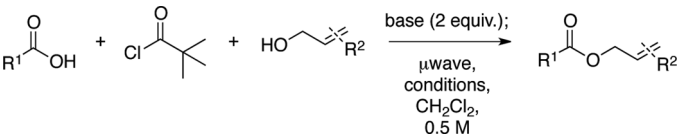
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.640970

Taylor & Francis
Taylor & Francis Group

MILD, RAPID, AND INEXPENSIVE MICROWAVE-ASSISTED SYNTHESIS OF ALLYLIC AND PROPARGYLIC ESTERS

Monica A. Gill and Jeffrey M. Manthorpe
Department of Chemistry, Carleton University, Ottawa, Ontario, Canada

GRAPHICAL ABSTRACT



Abstract *A variety of allylic and propargylic esters were rapidly prepared via microwave heating of their corresponding mixed anhydride derived from pivaloyl chloride. The reaction conditions were modified to account for the sterics of the alcohol and the electronics of the carboxylic acid.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Allylic esters; esterification; microwave-assisted synthesis; mixed anhydride; propargylic esters

INTRODUCTION

The formation of esters is one of the most established and thoroughly studied reactions in organic chemistry.[1] Widely used techniques employ carbodiimides, phosphorous reagents such as BOP-Cl, activated esters, acid chlorides, or anhydrides. Allylic esters are a particularly important class of compounds because of their utility in an array of transformations, including allylic rearrangements,[2] such as the Claisen rearrangement,[3] metal-catalyzed allylic alkylations,[4] including decarboxylative allylations,[5] cycloadditions,[6] epoxidations,[7] and dihydroxylations.[8] However, allylic esters can be difficult to prepare[9] and handle because of their acid sensitivity and propensity toward nucleophilic substitution.[10]

Received November 7, 2011.
Address correspondence to Jeffrey M. Manthorpe, Carleton University, Department of Chemistry, 203 Steacie Building, 1125 Colonel By Drive, Ottawa, ON K1S 5B6, Canada. E-mail: jeffrey_manthorpe@carleton.ca

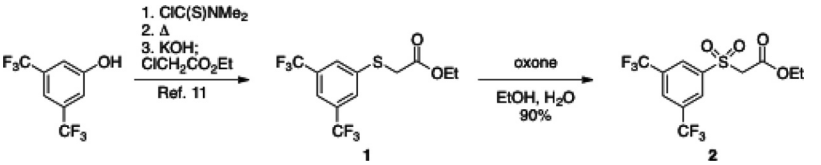
RESULTS AND DISCUSSION

As part of an ongoing research project, we required a facile route to allylic esters. We had ready access to ethyl ester **1** (Scheme 1)[11] and we first investigated the possibility of a titanium(IV) isopropoxide–catalyzed transesterification. As can be seen from Table 1, there was a considerable solvent effect in the reaction, with tetrahydrofuran (THF) promoting allyl ester formation but toluene suppressing it. Interestingly, the formation of isopropyl ester **6** was also observed and in some cases was the major product, particularly in toluene. Frustratingly, we were never able to obtain a sufficient conversion to the allyl ester to make this a viable pathway, even with very large excesses of allyl alcohol (**3**). Similar observations have been reported previously.[12] Attempts to transesterify the corresponding sulfone **2** offered no improvement. Use of boric acid catalysis[13] returned only starting material.

Ethyl ester **1** was cleanly saponified to afford α-thiacarboxylic acid **8**, which was used as our prototypical substrate (Scheme 2) as we sought to find a straightforward esterification method. To our consternation, this turned out to be far more challenging than anticipated. Our initial investigation (Table 2) explored the use of acid chloride **9** (entries 1 and 2) with heterogeneous and homogeneous bases, which afforded only modest yields of **4**. We also explored the esterification of acid **8** using diisopropylcarbodiimide (DIC). In the presence of catalytic amounts of dimethylaminopyridine (DMAP), DIC afforded **4** as a minor constituent of a complex mixture. The use of DIC with stoichiometric DMAP did not produce **4**. 2-Chloro-*N*-methylpyridinium iodide (Mukaiyama's reagent)[14] afforded only a small amount of the desired product in a complex mixture.

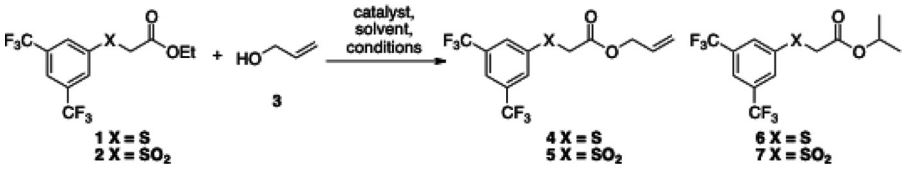
Given the failure of coupling agents, we then decided to explore the use of commercially available chloroformates to form mixed anhydrides, rationalizing that attack would occur preferentially on the carboxylate carbonyl (rather than on the carbonate carbonyl) of the mixed anhydride. In practice, ethyl chloroformate afforded only poor amounts of **4** when catalytic amounts of DMAP were used, and without DMAP only the ethyl ester **1** was observed, even in the presence of excess allyl alcohol (entries 3 and 4). Surprisingly, even the more electron-poor phenyl chloroformate heavily favored the phenyl ester **10** (entries 5 and 6). Use of di-*tert*-butyldicarbonate produced significant quantities of the highly hindered *tert*-butyl ester (entries 7 and 8).

Given the propensity of other nucleophiles to interfere with our desired acylation, we then opted to explore the use of a "true" mixed anhydride and drive the carbonyl regioselectivity via sterics. Thus we selected pivaloyl chloride (PivCl) as our mixed anhydride precursor. Unlike other acid chlorides used for mixed anhydride prepartion, such as 2,4,6-trichlorobenzoyl chloride,[15,16] PivCl is very inexpensive (~$18.50/mol), and the *tert*-butyl group provides significant steric hindrance. This



Scheme 1. Preparation of esters **1** and **2**.

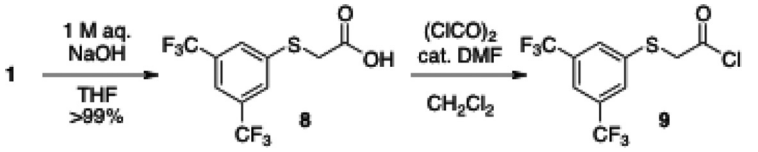
Table 1. Transesterification of esters **1** and **2**



Starting material	Equiv. **3**	Catalyst[a]	Solvent	Temp. (°C)	Time	1/2: 4/5: 6/7[b]
1	5	Ti(O-*i*-Pr)$_4$	THF	65	18 h	8:71:21
1	10	Ti(O-*i*-Pr)$_4$	THF	65	18 h	7:67:26
1	5	Ti(O-*i*-Pr)$_4$	PhMe	110	18 h	17:0:83
1	10	Ti(O-*i*-Pr)$_4$	PhMe	110	21 h	14:3:83
1	5	Ti(O-*i*-Pr)$_4$	THF	150 (μwave)	10 min	20:59:21
1	5	Ti(O-*i*-Pr)$_4$	THF	150 (μwave)	20 min	19:53:28
1	5	Ti(O-*i*-Pr)$_4$	THF	170 (μwave)	10 min	17:54:29
2	5	Ti(O-*i*-Pr)$_4$	CH_2Cl_2	40	18 h	14: 55: 31
2	10	Ti(O-*i*-Pr)$_4$	THF	65	21 h	0: 0: 100
2	5	Ti(O-*i*-Pr)$_4$	PhMe	110	21 h	18:7:75
2	10	Ti(O-*i*-Pr)$_4$	PhMe	110	21 h	11:5:84
2	5	Ti(O-*i*-Pr)$_4$	THF	150 (μwave)	10 min	12:60: 28
2	5	Ti(O-*i*-Pr)$_4$	THF	170 (μwave)	10 min	15:59:26
2	5	Ti(O-*i*-Pr)$_4$	THF	170 (μwave)	20 min	Partial decomposition
2	1.5	$B(OH)_3$	PhMe	110	5 h	100:0:0

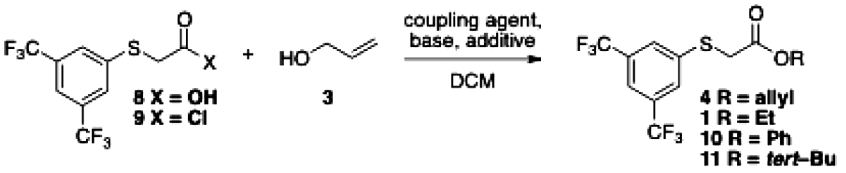
[a]Catalyst loading was 50 mol% for Ti(O-*i*-Pr)$_4$ and 10 mol% for $B(OH)_3$.
[b]Ratios determined by integration of ^{1}H NMR spectra of crude reaction mixtures.

approach led to clean formation of the allyl ester, both with and without catalytic amounts of DMAP (entries 9–11). This tactic presented several advantages: the major by-products (base, base hydrochloride, and pivalic acid) all can be readily removed by extraction or facile chromatography, and by using a mixed anhydride, we do not lose any of our desired acid component, unlike when a symmetrical anhydride is used.[10a] This has obvious implications for the use of complex and precious carboxylic acids. The undesired allylic pivalate **12** is formed by either incomplete mixed anhydride formation or addition of the alcohol to the more hindered carbonyl and can be removed by evaporation or chromatography. We evaluated the rate of mixed an hydride formation by combining acid **8**, PivCl, and pyridine in an NMR tube at 0.5 M in $CDCl_3$ and observed that both **8** and PivCl were consumed within 5 min, thus indicating that mixed anhydride formation is rapid and formation of **12** is due to diminished regioselecitivity.



Scheme 2. Preparation of acid **8** and acyl chloride **9**.

Table 2. Attempted esterification of **8** and **9**

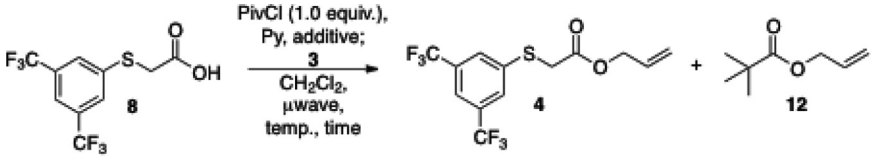


Entry	Starting material	Coupling agent	Equiv. **3**	Conditions	Result
1	**9**	None	3	K_2CO_3 (5 equiv.); CH_2Cl_2 (0.6 M), 0–23 °C, 18 h	**4** (40% yield)
2	**9**	None	3	Py (2 equiv.), DMAP (0.1 equiv.), CH_2Cl_2 (0.6 M), 0–23 °C, 18 h	Variable yields of **4** (40–60%)
3	**8**	Ethyl chloroformate (1.0 equiv.)	3	Py (2 equiv.), DMAP (0.1 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**4**:**1** 14:86
4	**8**	Ethyl chloroformate (1.0 equiv.)	3	Py (2 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**1** only
5	**8**	Phenyl chloroformate (1.0 equiv.)	3	Py (2 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 4 h	**4**:**10** 10:> 90 + unidentifiable impurities
6	**8**	Phenyl chloroformate (1.0 equiv.)	3	Py (2 equiv.), DMAP (0.1 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 4 h	**4**:**10** 12:88 + unidentifiable impurities
7	**8**	Boc_2O (1.1 equiv.)	3	Py (2 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**4**:**11** 70:30 + unidentifiable impurities
8	**8**	Boc_2O (1.1 equiv)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**4**:**11** 9:91 + unidentifiable impurities
9	**8**	Pivaloyl chloride (1.0 equiv.)	3	Py (2 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**4**:**8** 74:26
10	**8**	Pivaloyl chloride (1.0 equiv.)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH_2Cl_2 (0.1 M), 0–23 °C, 18 h	**4**:**8** 79:21
11	**8**	Pivaloyl chloride (1.0 equiv.)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH_2Cl_2 (0.1 M), reflux, 18 h	74% isolated **4**

At this point we optimized the reaction conditions (Table 3). A brief solvent screen showed no significant advantages to other solvents, and we therefore opted to stay with CH_2Cl_2; however, we did seek to shorten the reaction time. Given that the boiling point of CH_2Cl_2 is 40 °C, there is little room for accelerating the reaction by increasing the temperature. However, microwave heating in a sealed vial provides a rapid and simple approach to decreasing the reaction time.

One of the impressive features of this protocol is that it is effective with no excess of allyl alcohol; only 1 equivalent of acid, PivCl, and alcohol can be used without detriment to the regioselectivity (entries 1 and 2). In addition, the absence

Table 3. Optimization of esterfication of **8**



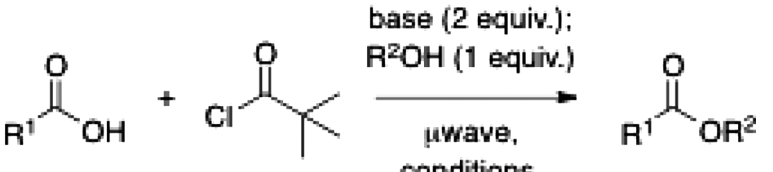
Entry	Equiv. ROH	Additive	Equiv. Py	Temp (°C)	Time (min)	Conc. **8** (M)	Ratio **4**:**12**	Isolated yield (%) **4**
1	2.0	10 mol% DMAP	2	100	10	0.1	70:30	n.d.
2	1.0	10 mol% DMAP	2	100	10	0.1	71:29	n.d.
3	1.0	No	2	100	10	0.1	79:21	58
4	1.0	No	2	120	10	0.1	74:26	n.d.
5	1.0	No	2	100	10	0.25	72:28	66
6	1.0	No	2	100	10	0.5	77:23	69
7	1.0	No	2	100	10	1.0	81:19	60
8	1.0	No	1	100	10	0.5	61:39	50
9	1.0	No	2[a]	100	10	0.5	11:89	n.d.
10	1.0	No	2	60	180	0.5	84:16	78
11	1.0	No	2	80	90	0.5	89:11	83
12	1.0	No	2	80	45	0.5	83:17	81
13	1.0	No	2	80	30	0.5	86:14	79
14	1.25	No	2	80	90	0.5	86:14	74
15	1.25	No	2	80	180	0.5	81:19	68

[a]2-Chloropyridine was used in place of pyridine.

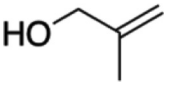
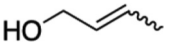
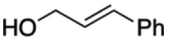
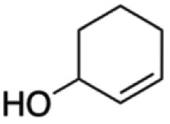
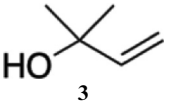
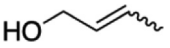
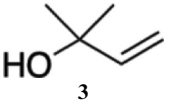
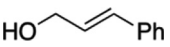
of catalytic amounts of DMAP improved the regioselectivity (entries 2 and 3). Increasing the reaction temperature from 100 to 120 °C led to a modest decrease in regioselectivity (entries 3 and 4). The optimal reaction concentration (entries 3 and 5–7) was found to be 0.5 M. Even though the regioselectivity was slightly greater at 1.0 M, the isolated yield of **4** was greatest at 0.5 M. 2-Chloropyridine was found to be insufficiently basic to effect efficient mixed anhydride formation and thus yielded primarily **12** via simple acylation of **3** by pivaloyl chloride. A screen of temperature and reaction time (entries 6 and 10–15) revealed that 80 °C for 90 min was optimal for both yield and regioselectivity.

With our optimized conditions in hand, we began to explore the scope of the reaction (Table 4). The reaction proved to be readily scalable to at least 2.0 g (6.6 mmol) of **8** (entry 2). In addition, a variety of allylic alcohols were successfully coupled with acid **8**, including 2- and 3-substituted primary alcohols (entries 3–5), as well as secondary and tertiary allylic alcohols (entries 6 and 7); however, the more electron-poor or sterically encumbered alcohols required longer reaction times to obtain comparable yields. We were also able to employ α-thiophenylacetic acid **13** (entries 8–10) as the carboxylic acid component under the same reaction conditions. When we moved to electronically neutral acid **14**, no desired product was obtained (entry 11). Fortunately this was readily remedied by changing the base from pyridine to DMAP and increasing the reaction temperature to 100 °C (entry 12). Similarly, benzoic acid **16** afforded poor results with pyridine, but again, replacement of pyridine with DMAP and increasing the reaction temperature resulted in increased yield.

Table 4. Scope of esterification protocol

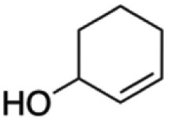
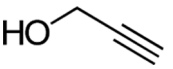
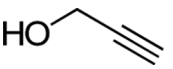
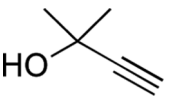
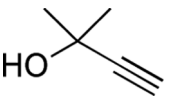


8 $R^1 = 3,5\text{-}(F_3C)_2C_6H_3SCH_2$
13 $R^1 = CH_2SPh$
14 $R^1 = CH_2CH(CH_3)_2$
15 $R^1 = PhCH_2CH_2$
16 $R^1 = Ph$

Entry	R^1CO_2H	R^2OH	Base	Conditions	Product	Yield (%)
1	**8**	**3**	Py	80 °C, 45 min	**4**	81
2	**8**	**3**	Py	80 °C, 45 min	**4**	86[a]
3	**8**		Py	80 °C, 90 min	**17**	80
4	**8**		Py	80 °C, 45 min	**18**	75
5	**8**		Py	80 °C, 90 min	**19**	76
6	**8**		Py	80 °C, 120 min	**20**	78
7	**8**		Py	80 °C, 120 min	**21**	73
8	**13**	**3**	Py	80 °C, 90 min	**22**	76
9	**13**		Py	80 °C, 90 min	**23**	73
10	**13**		Py	80 °C, 180 min	**24**	50
11	**14**	**3**	Py	80 °C, 90 min	**25**	0
12	**14**	**3**	DMAP	100 °C, 45 min	**25**	25[b]
13	**14**		DMAP	100 °C, 45 min	**26**	75
14	**15**	**3**	DMAP	100 °C, 45 min	**27**	76
15	**16**	**3**	Py	80 °C, 90 min	**28**	32
16	**16**	**3**	DMAP	80 °C, 45 min	**28**	63

(*Continued*)

Table 4. Continued

Entry	R^1CO_2H	R^2OH	Base	Conditions	Product	Yield (%)
17	**16**		DMAP	100 °C, 120 min	**29**	66
18	**8**		Py	80 °C, 90 min	**30**	74
19	**15**		DMAP	100 °C, 90 min	**31**	71
20	**8**		Py	80 °C, 180 min	**32**	56
21	**15**		DMAP	100 °C, 180 min	**33**	68

[a]Reaction conducted using 2.0 g (6.6 mmol) of **8**.
[b]The modest yield is ascribed to the volatility of **25**.

This methodology was successfully extended to incorporate the synthesis of propargylic esters (entries 18–21). The conditions optimized for allylic esters required little modification, as merely extending the reaction times produced the desired materials in reasonable yields.

In conclusion, we have developed a simple and rapid microwave-assisted method for the preparation of allylic and propargylic esters of a variety of carboxylic acids. While esterification is a well-studied field, a review of the literature shows that there are few esterification methods that use carboxylic acids and allylic or propargylic alcohols as starting materials, especially without excess of either the alcohol or acid component.[1] This approach is advantageous because many allylic alcohols are commercially available and can be used directly, rather than converted to allylic halides or haloformates. We believe that the results reported herein constitute a useful and practical contribution to the direct preparation allylic and propargylic esters, two challenging classes of compounds.

EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich (with the exception of 3,5-bistrifluoromethylphenol, from Matrix Scientific) and were used as received, without further purification. Microwave heating was performed in sealed vials in a Biotage Initiator 2.5 instrument with the absorption level set to ''normal''. Methylene chloride was distilled from CaH_2 prior to use. Crude products were analyzed by thin-layer chromatography (TLC) using glass-backed extra hard layer (60-Å) TLC plates from

Silicycle and visualized by fluorescence quenching under ultraviolet (UV) light and/or staining using potassium permanganate. Flash chromatographic purification of products was performed either on Silia-P Flash silica gel from Silicycle using a forced flow of eluent by the method of Still et al.[17] or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration in vacuo refers to rotary evaporation at 40 °C at the appropriate pressure. Yields refer to purified and spectroscopically pure compounds unless explicitly indicated as crude. NMR spectra were recorded on a Bruker Avance III 300 or Bruker AMX 400-MHz spectrometer. Chemical shifts are reported in parts per million (ppm). Tetramethylsilane (TMS) was used as the internal standard for ^{1}H and ^{13}C NMR spectra. ^{19}F NMR spectra are referenced to trifluorotoluene (−63.7 ppm). Infrared (IR) spectra were recorded on a Varian 1000 Scimitar Series or an ABB Bomem MB series spectrometer. Absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass Spectrometry Center. Compound **1** was prepared via a literature method.[11]

General Microwave Esterification Procedure

A Biotage microwave vial was charged with a Teflon-coated stirbar, carboxylic acid (1.0 equiv), and methylene chloride (0.5 M relative to carboxylic acid). The vial was sealed with a crimp-top lid equipped with a septum. In sequence, pivaloyl chloride (1.0 equiv), base (2.0 equiv), and alcohol (1.0 equiv) were added by syringe through the septum. In the case of solid bases or alcohols, the final sealing of the tube was delayed until addition was complete. The vial was heated for the indicated time at the indicated temperature in the microwave reactor. The reaction mixture was then diluted with diethyl ether, causing a white precipitate to form. This was washed with ice-cold 0.1 M H_2SO_4. The layers were separated, and the aqueous phase was extracted again with diethyl ether. The combined organic extracts were washed once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography using 5% EtOAc/hexanes.

Supporting Information Available

Detailed experimental procedures and characterization of acid **8** and esters **4** and **17** to **33** are available online in the Supplementary Information.

ACKNOWLEDGMENTS

This research has been supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation, the Ontario Research Fund, and Carleton University.

REFERENCES

1. (a) Otera, J. *Esterification*; Wiley-VCH: Weinheim, 2003; (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; pp. 484–491.

2. Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579–586.
3. For reviews of the Claisen rearrangement, see (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50; (b) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225; (c) Wipf, P. In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming and L. A. Paquette, (Eds.); Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2, pp. 827–874; (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452; (e) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1–252.
4. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (b) Lipshutz, B. *Synthesis* **1987**, 325–341; (c) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; G. Wilkinson, F. G. A. Stone and E. W. Abel (Eds.); Pergamon Press: Oxford, 1982; Vol. 8, Chapter 57, p. 713; (d) Godleski, S. A. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming (Eds.); Pergamon Press: New York, 1991; Vol. 4, Chapter 3.3.
5. Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846–1913.
6. (a) Roush, W. R. *Adv. Cycloaddit.* **1990**, *2*, 91; (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; (c) Helquist, P. In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming and M. F. Semmelhack (Eds.); Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.6.
7. Rossiter, B. E. In *Asymmetric Synthesis*; J. D. Morrison (Ed.); Academic Press: Orlando, FL, 1985; Vol. 5, pp. 193.
8. For reviews, see: (a) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761–1795; (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
9. For recent examples of the preparation of allylic esters, see (a) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206–1207; (b) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875–3578; (c) Hodgson, D. M.; Arif, T. *Org. Lett.* **2010**, *12*, 4204–4207.
10. (a) Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775–14779, and references cited therein; (b) Brady, D. G. *J. Chem. Soc. D, Chem. Commun*. **1970**, 434–435; (c) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687–3696.
11. (a) Alonso, D.; Nájera, D.; Varea, M. *Helv. Chim. Acta* **2002**, *85*, 4287–4305; (b) Samreth, S.; Millet, J.; Bellamy, F.; Bajgrowicz, J.; Barberouse, V.; Renault, P. Nouveaux β-D-phényl-thioxylosides, leur procédé de preparation et leur utilisation en thérapeutique. European Patent 0365397 A2, April 25, 1990.
12. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138–141.
13. Kondalah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Huge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. V. *Tetrahedron Lett.* **2008**, *49*, 106–109.
14. (a) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045–1048; (b) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166; (c) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863–1866; (d) Armstrong, A.; Wang, Y.; Wang, P. 2-Chloro-1-methylpyridinium iodide. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*: Wiley. Available at http://onlinelibrary.wiley.com/o/eros/articles/rc126/pdf_fs.html
15. 2,4,6-Trichlorobenzoyl chloride is available from Aldrich for ~$3500/mol.
16. Ewin, R. A. 2,4,6-Trichlorobenzoyl chloride in *e-EROS Encyclopedia of Reagents for Organic Synthesis*: Wiley. Available at http://onlinelibrary.wiley.com/o/eros/articles/rt201/pdf_fs.html
17. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.