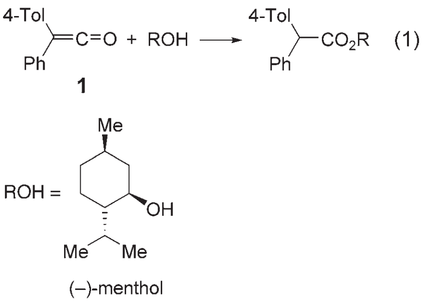
DOI: 10.1002/anie.200501849

Catalytic Asymmetric Esterification of Ketenes**

Thomas T. Tidwell*

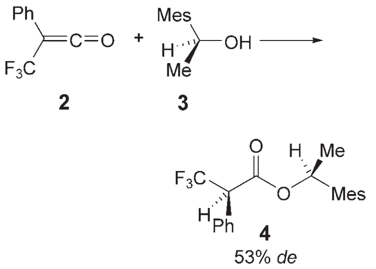
Keywords:
asymmetric catalysis · enol esters · homogeneous catalysis · ketenes

Ester formation by addition of alcohols to ketenes was discovered 100 years ago, when Hermann Staudinger prepared diphenylketene as the first isolated member of this versatile and reactive family, and by reaction with ethanol formed the ethyl ester of diphenylacetic acid.[1a] As soon as unsymmetrical disubstituted ketenes were prepared it became apparent that esterification of these ketenes by alcohols generates a new chiral center, and by 1919 an attempt was made by Weiss to achieve asymmetric synthesis in this reaction, by the addition of the optically active alcohol (−)-menthol to phenyl(4-tolyl)ketene (**1**) [Eq. (1)].[1b] This report attracted considerable attention at the time and was initially accepted, but upon reexamination it was agreed there was no selectivity in the formation of the new stereocenter.[1c–e] This was an unsuitable substrate and an improbable outcome, as the only difference between the two aryl groups is the 4-methyl substituent in one aryl ring, which would have an imperceptible effect on proton transfer forming the new chiral center. However, the goal of achieving stereoselectivity in ketene esterification has been a major challenge for synthetic chemistry ever since, especially in view of the prominent bioactivity of many 2-arylalkanoic acids that are potentially available by this reaction.



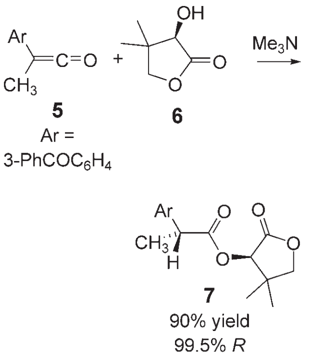
(1)

The search for stereoselectivity using this methodology received new impetus with a prominent report of the reaction of phenyl(trifluoromethyl)ketene (**2**) with several chiral alcohols including **3** (Mes = 2,4,6-trimethylphenyl) which formed **4** with significant 53 % stereoselectivity, and showed the way to reach the goal envisaged by Weiss [Eq. (2)].[2]



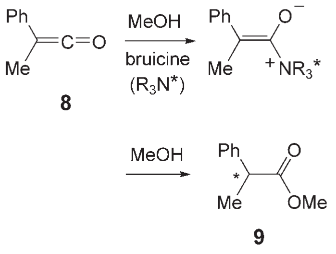
(2)

This path for asymmetric synthesis by ketene esterification using chiral alcohols was pursued at the Merck laboratories, where the addition of the chiral alcohol (*R*)-pantolactone (**6**) to ketene **5** was found to give 2-arylpropionate **7** with 99.5 % diastereoselectivity [Eq. (3)].[3a] The origins of the selectivity in this reaction have been elucidated by computational means using (*S*) methyl lactate as a model.[3b] Many variations on this reaction have been reported, including the use of a polymer-bound analogue of pantolactone.[3]



(3)

The use of chiral catalysts to induce stereoselectivity in ketene esterification offers an attractive alternative to the use of stoichiometric chiral alcohols to achieve this result, and a major achievement in this quest came in 1960 when the brucine-catalyzed stereoselective addition of methanol to phenyl(methyl)ketene (**8**) forming the ester **9** was reported by Pracejus [Eq. (4)].[4a]



(4)

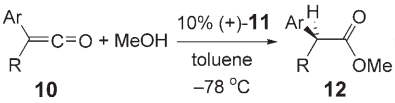
The selectivity was temperature dependent, ranging from 25 % *ee* for the *S* ester at −110 °C to 10 % *ee* for the *R* ester at 80 °C.[4a] This was improved to 76 % *ee* for the *S* ester when benzoylquinine was used at −110 °C.[4b,c] This discovery invited further improvements in the enantioselectivity using new catalysts,[4d–f] but it was a long wait before this was to take place.

---

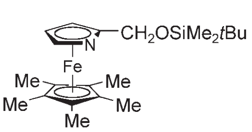
[*] Prof. T. T. Tidwell
Department of Chemistry
University of Toronto
Toronto, ON M5S3H6 (Canada)
Fax: (+1) 416-978-3585
E-mail: ttidwell@chem.utoronto.ca

[**] Financial support by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged

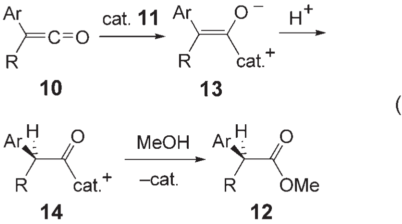
Then in 1999 Fu and co-workers introduced a designed catalyst to supplement the use of cinchona alkaloids for the catalytic asymmetric synthesis of esters from ketenes. They reported that addition of methanol to aryl(alkyl)ketenes **10** catalyzed by the azaferrocene catalyst **11** in the presence of 2,6-di(*tert*-butyl)pyridinium triflate gave up to 80% *ee* in the formation of esters **12** [Eq. (5)].[5a] It was proposed that this reaction took place by a catalytic cycle with nucleophilic attack of the catalyst on the ketene forming the enolate **13**, which was protonated by the pyridinium triflate to form **14** stereoselectively, and then methanol displaced the catalyst to give the ester **12** [Eq. (6)].[5a]



(5)

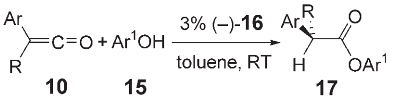


(+)-**11**

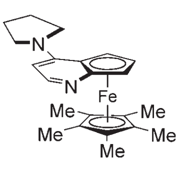


(6)

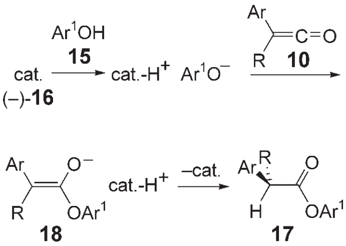
This procedure was further improved for the esterification of ketenes **10** by phenols **15** using the second-generation catalyst **16**. Aryl esters **17** were obtained with a selectivity of 35–91% *ee*, and the highest *ee* value was achieved with 2-*tert*-butylphenol [Eq. (7)].[5b] Reactions of a variety of ketenes with this phenol gave *ee* values of 79–94% and yields of 66–97%. The mechanism proposed for this process is different than that for the addition of methanol and involves deprotonation of the phenol, followed by phenoxide attack on the ketene forming enolate **18**, and proton transfer from the resulting ion pair forming **17** [Eq. (8)].[5b]



(7)

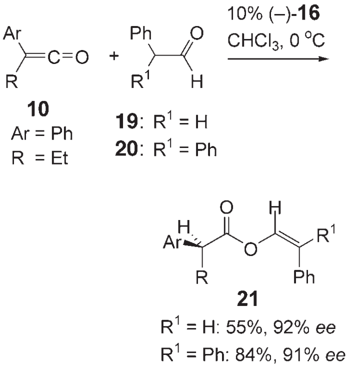


(−)-**16**

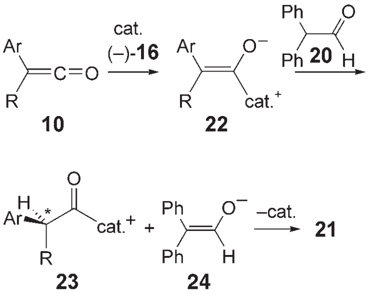


(8)

In a novel and unexpected extension of the search for catalyzed stereoselective esterification of ketenes, Schaefer and Fu have now discovered that alkyl(aryl)ketenes **10** react with the readily enolizable aldehydes **19** and **20** with catalysis by (−)-**16** to give stereoselective formation of enol esters **21** [Eq. (9)].[5c] The reaction of phenyl(ethyl)ketene and diphenylacetaldehyde resulted in the formation of **21** in 84% yield and 91% *ee*. For other ketenes the reaction was even more successful; the reaction of 2-tolyl(ethyl)ketene gave 99% yield and 98% *ee* (Table 1).[5c]



(9)

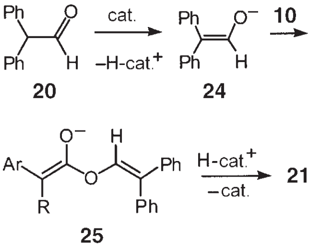


(10)

Two possible mechanisms were proposed for this reaction, namely, initial addition of the catalyst to the ketene giving **22**, which stereoselectively abstracts a proton from the aldehyde giving **23**, which combines with the aldehyde enolate **24** [Eq. (10)]. Alternatively, addition of **24** to the ketene gives **25**, which is converted to **21** by stereoselective proton transfer by the protonated catalyst [Eq. (11)].[5c]

The use of diphenylacetaldehyde (**20**) is a shrewd choice for this reaction, as it exists in the enol form ($pK_a = 9.4$) to the extent of 10% in aqueous solution at 25°C.[6] Interestingly this is the same pK_a as for phenol and suggests that the mechanism of Equation (11), which resembles that of Equation (8) found for phenols, may be preferred.

There is precedent for the O-acylation of ketone enolates by ketenes,[7a–c]

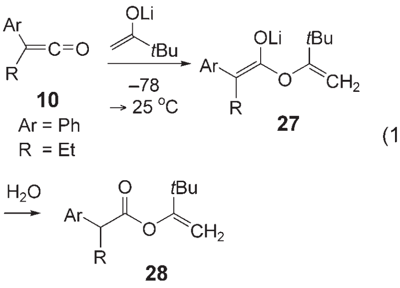


(11)

Table 1: Stereoselective formation of vinyl esters from ketenes **10** and diphenylacetaldehyde (**20**) [Eq. (9)].[5c]

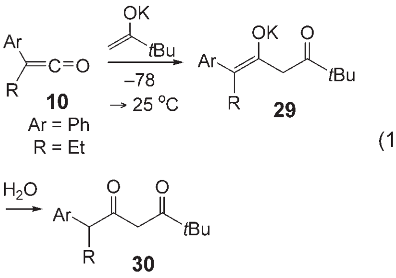
10		**21**		**10**		**21**	
Ar	R	Yield [%]	*ee* [%]	Ar	R	Yield [%]	*ee* [%]
Ph	Me	74	78	Ph	*t*Bu	96	88
Ph	Et	84	91	2-Tol	Et	99	98
Ph	*i*Bu	81	77	2-MeOC_6H_4	Me	95	97
Ph	*i*Pr	95	98	4-MeOC_6H_4	Et	89	92
Ph	*c*Pent	99	97	4-ClC_6H_4	Et	96	88

including the involvement of ester enolates in the polymerization of dimethylketene.[7a] Also the reaction of phenyl(ethyl)ketene with lithium pinacolate at −78 °C followed by warming to 25 °C and protonation with water gave the enol ester **28** in 57 % yield, evidently through the intermediacy of the enolate **27** [Eq. (12)].[7c] When the potassium enolate was reacted similarly, the diketone **30** from acylation on carbon was the observed product, indicating the intermediacy of the enolate **29** [Eq. (13)].[7c] Rearrangement of the initially formed enolates was also shown to occur.[7c] Catalyst **16** is reported not to promote rearrangement of the enol esters **21** formed in Equation (9) to 1,3-dicarbonyl compounds.[5c]



(12)

The unique features of the work by Schaefer and Fu suggest myriad possible extensions of their work. The enol esters derived from this reaction undergo facile hydrolysis to give chiral carboxylic acids, but this is wasteful of the interesting enol ester functionality contained in the molecule. Possibly stereoselective addition to the carbon–carbon double bond of the esters generating useful new functionality could be achieved. Other easily enolized carbonyl functions such as 1,3-dicarbonyl compounds or fluorinated ketones may be susceptible to this methodology. Further progress in this area can be expected.



(13)

---

[1] a) H. Staudinger, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1735–1739; b) R. Weiss, *Monatsh. Chem.* **1919**, *40*, 391–402; c) A. McKenzie, E. W. Christie, *J. Chem. Soc.* **1934**, 1070–1075; d) J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, Prentice Hall, New York, **1971**, pp. 276–281, 295, 322, 326; e) For a historical summary of the beginnings of ketene chemistry see T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 5926–5933; *Angew. Chem. Int. Ed.* **2005**, *44*, 5778–5785.

[2] E. Anders, E. Ruch, I. Ugi, *Angew. Chem.* **1973**, *85*, 16–20; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 25–29.

[3] a) R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1989**, *111*, 7650–7651; b) C. E. Cannizzaro, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 10992–11008; c) R. Akkari, M. Calmes, N. Mai, M. Rolland, J. Martinez, *J. Org. Chem.* **2001**, *66*, 5859–5865.

[4] a) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22; b) H. Pracejus, G. Kohl, *Justus Liebigs Ann. Chem.* **1969**, *722*, 1–11; c) H. Pracejus, *Fortsch. Chem. Forsch.* **1967**, *8*, 493–553; d) H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480–518; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477–515; e) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726–2748; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566–2587; f) R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545–3565.

[5] a) B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637–2638; b) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177; c) C. Schaefer, G. C. Fu, *Angew. Chem.* **2005** *117*, 4682–4684; *Angew. Chem. Int. Ed.* **2005**, *44*, 4606–4684.

[6] Y. Chiang, A. J. Kresge, E. T. Krogh, *J. Am. Chem. Soc.* **1987**, *109*, 2600–2607;

[7] a) K. Yoshida, Y. Yamashita, *Tetrahedron Lett.* **1966**, *7*, 693–696; b) H. O. House, R. A. Auerbach, M. Gall, N. P. Peet, *J. Org. Chem.* **1973**, *38*, 514–522; c) L. Gong, R. Leung-Toung, T. T. Tidwell, *J. Org. Chem.* **1990**, *55*, 3634–3639.