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Catalytic Michael Reactions of Ketoesters with a Camphor-Derived Acrylate Equivalent: Stereoselective Access to All-Carbon Quaternary Centers

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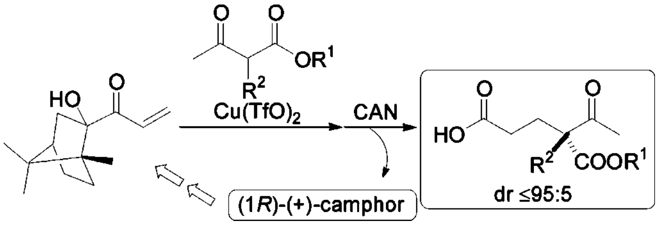
ABSTRACT



A camphor-based α′-hydroxy enone reagent acts as a chiral acrylate equivalent in copper-catalyzed Michael reactions of *β*-keto esters and affords products that possess all-carbon quaternary stereocenters of high enantiomeric purity.

All-carbon quaternary stereocenters pose a particular challenge for synthesis because of steric repulsion between the carbon substituents in the product and the difficulty in achieving good stereocontrol.[1] Nowadays the construction of a quaternary stereocenter remains the touchstone of every stereoselective procedure and a significant challenge in the total synthesis of natural products. One versatile access to all-carbon quaternary stereocenters relies on the conjugate addition reaction of soft C-nucleophiles to acceptor-activated olefins,[2] and within this strategy both asymmetric catalysis with preformed silyl enolates[3] and metal-catalyzed reactions involving preformed chiral enamides[4] have been reported. Direct catalytic methods involving stabilized enolates have also been documented recently by using both asymmetric

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[⊥] X-ray analyses.

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(1) For recent reviews, see: (a) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (e) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (f) Trost, B. M.; Chunhui, S. *Synthesis* **2006**, 369–396. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.

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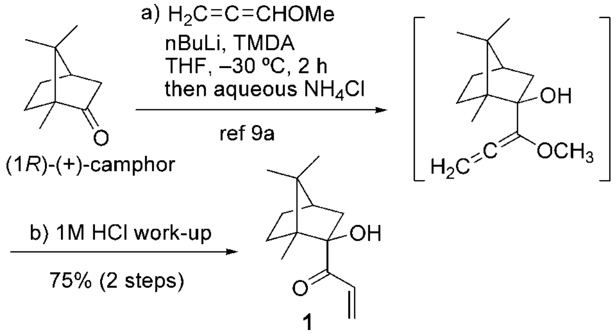
organocatalysts[5] and metal catalysts.[6] Despite these advances, currently available methods are restricted to certain combinations of substrate nucleophile and electrophile, most often involving vinyl ketones, vinyl sulfones, enals, nitroalkenes, and substituted acrylonitriles as the electrophilic component. Although the corresponding conjugate addition products from acrylic acid derivatives bear significant synthetic interest, this process is virtually undeveloped yet.[7] Here we present a highly stereoselective direct Michael reaction of α-substituted *β*-keto esters and a chiral acrylate equivalent,[8] easily prepared from camphor, as a new entry to all-carbon quaternary stereocenters of high enantiomeric purity.

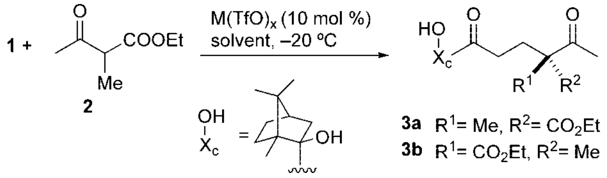
We have previously documented that α′-hydroxy enone **1**, accessible from (1*R*)-(+)-camphor in multigram quantities through a one-pot two-step sequence, Scheme 1, is able to impart remarkable levels of diastereofacial selectivity in Diels−Alder reactions of inherently poor reactivity and diastereoselectivity.[9] Further demonstration of the potential of the α′-hydroxy enone template in metal-assisted transformations[10] was ascribed to the capacity of the ketol moiety for 1,4-metal binding.[11] We argued that such a stereochemical constrain might be effective for substrate activation and chirality transfer during generation of quaternary stereocenters.

Scheme 1



To evaluate this assumption, initial screening reactions were carried out with **1** and ethyl 2-methylacetoacetate **2** in the presence of several metal triflates, Table 1. Data revealed that $Cu(TfO)_2$ gave the best results, and the addition adduct **3** could be obtained as an isomeric mixture with a ratio of

Table 1. 1,4-Addition of Ethyl 2-Methylacetoacetate to α′-Hydroxy Enone **1** Catalyzed by Metal Triflates[a]



entry	$M(TfO)_x$	additive	solvent	dr[b]	yield, %[c]
1	**$Cu(TfO)_2$**		**CH_2Cl_2**	**86:14**	**78**
2				76:24	
3		4Å MS	CH_2Cl_2	80:20	
4		**4Å MS**		**90:10**	**91**
1	$Mg(TfO)_2$			50:50	81
2	$Zn(TfO)_2$			60:40	85
5	$Yb(TfO)_3$			60:40	80
6	$La(TfO)_3$			50:50	92
7	$Sc(TfO)_3$			55:45	80

[a] All reactions were run at 0.5 mmol scale until consumption of starting enone. [b] Diastereomeric ratios were determined by ^{13}C NMR. [c] Product purified by column chromatography.

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(7) For remarkable exceptions, see: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205. (b) Balskus, E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810–6812. See also ref 3b.

(8) A chiral acrylate derived from (−)-8-phenylmenthol has been used in the asymmetric 1,4-addition of ethyl 2-oxocyclohexanecarboxylate catalyzed by trifluoromethanesulfonic acid (dr 69:31). Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770–3773.

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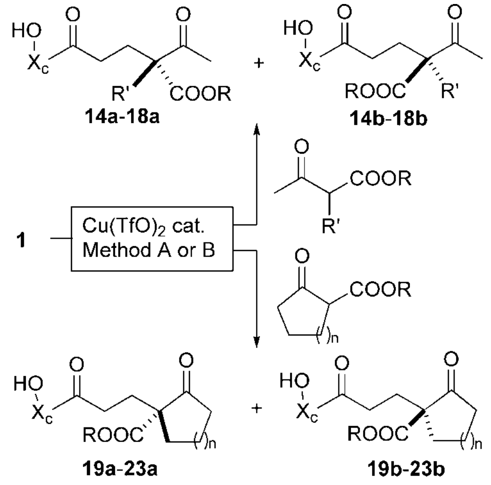
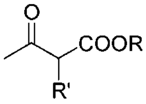
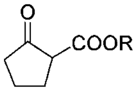
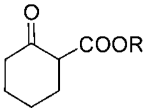
(10) (a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943. (b) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *125*, 9188–9189. (c) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155. (d) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187–6190. (e) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161–1164. Also, see: (f) Lee, S.; Lim, C. J.; Kim, S.; Subramaniam, R.; Zimmerman, J.; Sibi, M. P. *Org. Lett.* **2006**, *8*, 4311–4313. (g) Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 2867–2870.

Table 2. 1,4-Addition of Acyclic and Cyclic β-Keto Esters to α′-hydroxy Enone **1** Catalyzed with Copper Triflate[a]



keto ester		R	R'	prod.	method	**a**:**b**[b]	yield %[c]
	**4**	^{i}Pr	Me	**14**	A	91:9	73
					B	86:14	70
	5	Bn	Me	**15**	B	85:15	67
	6	^{t}Bu	Me	**16**	A	93:7	90
					B	86:14	98
	7	^{t}Bu	Et	**17**	B	95:5	57
	8	^{t}Bu	Bn	**18**	B	88:12	50
	**9**	Me		**19**	B	76:24	77
	10	Et		**20**	A	60:40	96
					B	80:20	98
	11	^{t}Bu		**21**	A	95:5	98
	**12**	Et		**22**	B	91:9	93
	13	^{t}Bu		**23**	B	95:5	55

[a] Methods A and B as defined in ref 13. [b] Diastereomeric ratios were determined by ^{13}C NMR. [c] Yield of isomeric mixture purified by column chromatography.

86:14. The reactions were typically carried out in dichloromethane as solvent using 10 mol % catalyst at −20 °C, with lower temperatures giving no significant changes. Other solvents tested, such as THF, Et_2O, or toluene, led to lower selectivity, and the reaction did not proceed at all in acetonitrile. When the reaction was carried out without added solvent and using the β-keto ester as the solvent media, an isomeric mixture with a ratio of 76:24 was produced. Metal Lewis acids other than triflates, such as $ReCl_5$, AuCl, $Ni(ClO_4)_2{\cdot}6H_2O$, $FeCl_3{\cdot}6H_2O$, $PdCl_2(CH_3CN)_2$, $Zn(ClO_4)_2{\cdot}6H_2O$, and $RuCl_3{\cdot}nH_2O$, were also tested, but poor yields and stereoselectivities were attained. Because of the fact that molecular sieves have shown high efficiency in a variety of Lewis acid catalyzed stereoselective processes,[12] we carried out the reaction with $Cu(TfO)_2$ in the presence of this additive. In this case the diastereomeric ratio decreased to 80:20, but surprisingly, when the β-keto ester was used as solvent, the isomeric mixture obtained rose to a 90:10 ratio.

To define the scope of this reaction, we next examined various β-keto esters. Table 2 shows the results obtained in the Michael reaction of α′-hydroxy enone **1** with several cyclic and acyclic α-substituted β-keto esters using dichloromethane as the solvent (method A) or the β-keto ester as the solvent in the presence of molecular sieves (method B).[13] In general, Michael adducts were obtained in good yields and with diastereomeric ratios ranging from 85:15 to 95:5 for the acyclic α-substituted β-keto esters. Noteworthy is the use of the sterically demanding α-alkyl *tert*-butyl β-keto esters **6** and **7**, which afforded products with diastereomeric ratios of 93:7 and 95:5, respectively, whereas *tert*-butyl 2-benzylacetoacetate **8** yielded a mixture of isomers in an 88:12 ratio. The configuration of adduct **14a** was established by single-crystal X-ray structure analysis,[14] and the configurations of the remaining acyclic adducts **3** and **15**−**18** were assigned by analogy.

Cyclic β-keto esters **9**−**13** behave similarly, and as shown in Table 2, *tert*-butyl esters **11** and **13** afforded the corresponding adducts with excellent diastereomeric ratios (95:5). Likewise, a single-crystal X-ray structure analysis of compound **23a** corroborated the assigned configurations of the adducts.

The excellent diastereoselectivity observed in these reactions is of particular interest in that it provides, through oxidative cleavage of the acyloin moiety, carboxylic acids with a quaternary stereocenter in good chemical yields and enantiomeric purities. For example, treatment of isomeric mixtures of adducts **14**, **16**, and **23** with cerium ammonium nitrate (CAN) gave the corresponding carboxylic acids **24**, **25**, and **26** in high yields and ee's, Scheme 2. On the other hand, separation of diastereomeric adducts through crystallization or chromatography opens a route to final products of almost perfect enantiopurity. For instance, separation of **23a** by column chromatography and subsequent acyloin cleavage led to **26** in essentially optically pure form. The whole transformation represents a formal 1,4-addition to acrylic acid derivatives with concomitant generation of all-carbon quaternary stereocenters in high selectivity. In addition, both carboxy groups in the products are orthogonal. Importantly, in each case, the starting source of chiral information, (1*R*)-(+)-camphor, is easily recovered from the reaction mixture almost quantitatively and without loss of optical integrity.[15]

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(11) See ref 10a,b. For early formulation of the 1,4-metal binding activation model of ketols, see: Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441–4444.

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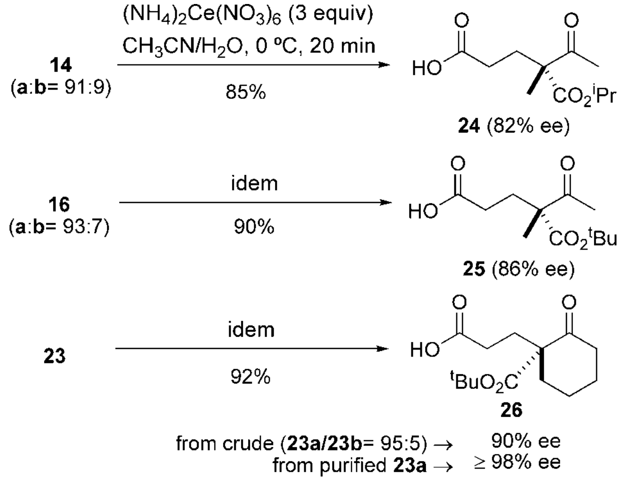
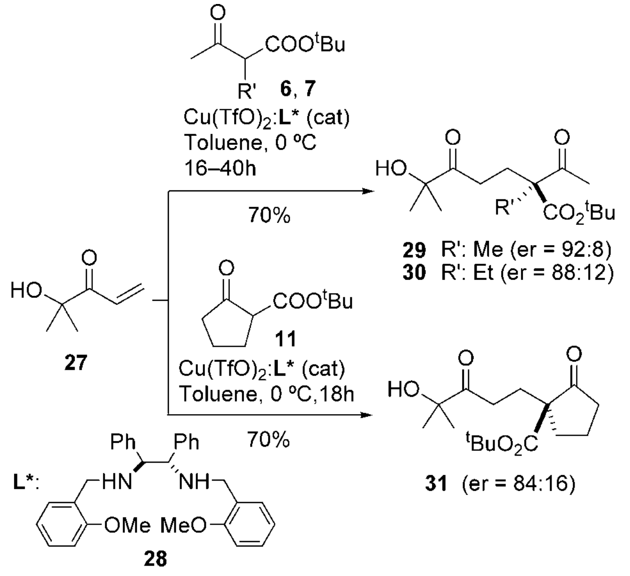
(13) **Experimental Procedure. Method A.** A solution of vinyl ketone **1** (0.1042 g, 0.5 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise to a mixture of copper(II) triflate (0.0181 g, 0.05 mmol) and the β-keto ester (1 mL) in 0.4 mL of CH_2Cl_2 at −20°C. The reaction mixture was stirred at the same

Scheme 2



Scheme 3



Finally, we decided to assess the possibility of implementing an enantioselective version of the method by using the achiral α′-hydroxy enone **27**[10] and a chiral copper catalyst. Initial exploration revealed chiral diamines as the best-suited ligands for this catalytic process. For example, the copper-catalyzed reaction of **27** and both acyclic ketoesters **6** and **7**, and cyclic ketoester **11**, using diamine **28** as a ligand[16] in toluene at 0 °C, afforded the corresponding Michael adducts **29**, **30**, and **31** with high yield and enantiomeric ratios, Scheme 3. Oxidation of the products with CAN as above yielded the corresponding carboxylic acids with acetone being the only byproduct formed, an additional aspect of the approach that is of practical interest.

In summary, a copper-catalyzed highly diastereoselective direct 1,4-addition of α-substituted *β*-keto esters to a chiral acrylate equivalent derived from (1*R*)-(+)-camphor is presented. Upon smooth removal of the auxiliary, which can be reused, differently functionalized molecules bearing all-carbon quaternary stereocenters are obtained in high enantiomeric purity. Extension of this model to other Michael reactions is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures; characterization data for compounds **1**, **3a**, **14a**−**23a**, **24**−**26**, and **29**−**31**; representative ^{1}H and ^{13}C NMR spectra and HPLC chromatograms; X-ray data for **14a** and **23a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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temperature overnight. Then, CH_2Cl_2 (5 mL) was added, and the resulting solution was washed twice with 5 mL of water. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant EtOAc/hexane 1:10). The diastereomeric ratio was determined in each case by ^{13}C NMR analyses and in some cases by HPLC analyses. Purification to obtain the major diastereomer was effected by flash column chromatography, using a 1:20 EtOAc/hexane mixture as the eluant. **Method B.** Vinyl ketone **1** (0.1042 g, 0.5 mmol) was added to a mixture of copper(II) triflate (0.0181 g, 0.05 mmol), molecular sieves 4Å powder (100 mg), and the *β*-keto ester (1 mL) at −20°C. The reaction mixture was stirred at the same temperature overnight. The same workup and purification procedure of Method A was followed.

(14) See Supporting Information.

(15) (1*R*)-(+)-Camphor: Aldrich $[\alpha]^{25}_D$ +42.2 (*c* 1.0 in EtOH). Recovered material, $[\alpha]^{25}_D$ +41.5 (*c* 1.0 in EtOH).

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