

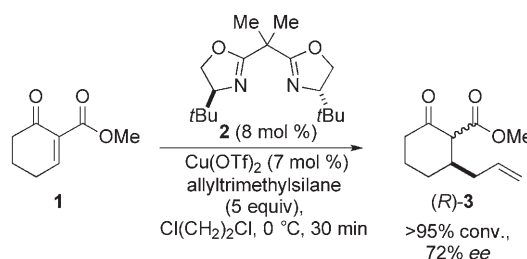
Catalytic Enantioselective Hosomi–Sakurai Conjugate Allylation of Cyclic Unsaturated Ketoesters**

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Despite impressive advances over the years,^[1] there are still important transformations that lack catalytic asymmetric variants. While Lewis acid catalyzed additions of allylsilanes to carbonyl compounds^[2] and acetals^[3] have been well studied using catalytic,^[4] as well as auxiliary-based methods to control absolute configuration,^[5] to the best of our knowledge, there are no effective methods for catalyzing the asymmetric 1,4-addition of allyltrimethylsilane to unsaturated carbonyl compounds.^[6] In that regard, we report herein a catalytic enantioselective conjugate addition of allyltrimethylsilane to various activated cyclic enones with selectivities surpassing 98% *ee*. The 1,4-addition of the air- and moisture-stable nucleophile to unsaturated carbonyl compounds proceeds to >95% conversion in the presence of Cu(OTf)₂ (10 mol%) with the commercially available di(*tert*-butyl)bis(oxazoline) (box) ligand (**2**).^[7] We show how these products can be functionalized to a variety of useful enantiomerically enriched systems.

Our initial studies into the development of a chiral Lewis acid catalyst indicated that simple cyclic and acyclic α,β -unsaturated carbonyls (ketones and esters) did not react with a variety of metal–ligand combinations.^[8] We therefore sought to activate the substrate by installation of a second electron-withdrawing/chelating group at the α -position of the enone (i.e., **1**). In the presence of Cu(OTf)₂ (7 mol%) and bis(oxazoline) ligand **2** (8 mol%) in Cl(CH₂)₂Cl, we obtained the desired 1,4-allyl-addition product **3** in >95% conversion (after 30 min at 0 °C) and 72% *ee* as a mixture of keto–enol tautomers (Scheme 1). Alternative solvents (CH₂Cl₂, Et₂O, toluene, EtOAc, etc.) and metal salts, including other copper salts, resulted in lower selectivities.^[9] Other chiral ligands (e.g., peptide-based,^[10] salen,^[11] Trost ligand^[12]) led to high conversion (>95%), but with low selectivity (<5% *ee*).

To identify a more effective catalyst, we prepared and screened approximately 40 mono- and bis(oxazoline) ligands. A selection of the bis(oxazoline) ligands studied are illustrated in Table 1. Phenylglycine- and phenylalanine-derived ligands (**7** and **8**, respectively) gave high conversions, but low



Scheme 1. Copper/box-catalyzed asymmetric allylation of activated enone substrate **1**.

Table 1: Ligand evaluation studies for an enantioselective Hosomi–Sakurai conjugate allylation.^[a]

Entry	Ligand	R ¹	R ²	Conv. [%]	<i>ee</i> [%]
1	4	H	<i>t</i> Bu	> 95	11
2	2	CH ₃	<i>t</i> Bu	> 95	72
3	5	-(CH ₂) ₂ -	<i>t</i> Bu	> 95	70
4	6	-(CH ₂) ₃ -	<i>t</i> Bu	> 95	70
5	7	CH ₃	Ph	> 95	10
6	8	CH ₃	Bn	> 95	< 5
7	9	–	–	> 5	n.d. ^[b]
8	10	–	–	> 95	38

[a] The reaction and conditions used are shown in Scheme 1, except the reaction time was 14 h. [b] Not determined.

enantioselectivities were observed (Table 1, entries 5 and 6). Modifying the *gem*-dimethyl head group of ligand **2** to a cyclopropyl (**5**) or cyclobutyl head group (**6**) has been reported to change the bite angle at the metal center, often with drastic changes in selectivity.^[13] In this case, however, these modifications had minimal effects on the selectivity (72% *ee* with **2** vs. 70% *ee* with **5** and **6**, Table 1, entries 3 and 4). A methylene linker was also examined, but the selectivity dropped significantly to 11% *ee* (Table 1, entry 1). A tridentate Py-box ligand **9**,^[14] bearing an additional Lewis basic moiety, resulted in diminished conversion (Table 1, entry 7). We also tested unsymmetrical bis(oxazoline) and mono(oxazoline) ligands.^[9] Ligand **10** delivered the desired product efficiently, but in low enantioselectivity (38% *ee*, Table 1, entry 8). Shorter and longer linkers between the oxazoline

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[**] Support from the NIH (GM-57212) is gratefully acknowledged. We thank the Hoveyda group for use of their chiral GLC and HPLC. We also thank Prof. James Morken for helpful discussions.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

rings were introduced, such as in oxalate- and phthalic acid-derived ligands; however, these ligands did not lead to improved results compared to ligand **2**.^[9] In addition, we also investigated the effect of additives upon the reaction.^[15] Various desiccants (e.g., molecular sieves, MgSO₄), as well as Lewis basic additives were tested, yet none of these resulted in enhanced selectivities.^[9]

We found that the enantioselectivity could be improved by changing the solvent to CH₂Cl₂, thus allowing for lower reaction temperatures. When run at –78 °C in CH₂Cl₂, with ligand **2** (11 mol %) and Cu(OTf)₂ (10 mol %), product **3** was obtained in 78 % yield and 90 % *ee* (Table 2, entry 1; cf. Table 1, entry 2).

Table 2: Copper-catalyzed enantioselective Hosomi–Sakurai conjugate allylation of unsaturated ketoesters.^[a]

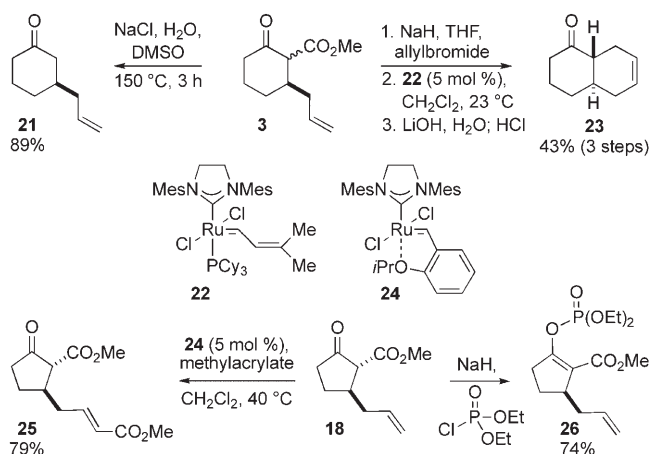
Entry	Enone	Product	<i>t</i> [h] (<i>T</i> [°C])	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1 ^[d]			45 (–78)	78	90
2 ^[e]			48 (–50)	65	97
3 ^[f]			15 (0)	51	55
4 ^[f]			38 (23)	77 ^[c]	64
5 ^[g]			15 (–78)	69	70
6 ^[d]			17 (23)	65	> 98

[a] Yields of isolated products after silica gel chromatography. [b] Determined by GLC or HPLC with a chiral stationary phase; see the Supporting Information for details. [c] Yields of isolated products after decarboxylation of the ester (2 steps). [d] Conditions: **2** (11 mol %), Cu(OTf)₂ (10 mol %), allyltrimethylsilane (5 equiv) in CH₂Cl₂, N₂. [e] CH₂Cl₂/Cl(CH₂)₂Cl (5:1) as solvent. [f] Cl(CH₂)₂Cl as solvent. [g] 3 equiv of allyltrimethylsilane.

With this optimal chiral catalyst, we examined the scope of the catalytic enantioselective Hosomi–Sakurai allylation (Table 2). Five-, six-, and eight-membered ring substrates were effectively allylated with commercially available allyltrimethylsilane. The six-membered ring enone **11**, with *gem*-dimethyl substitution at the 6-position, gave excellent enantioselectivity (97 % *ee*, 65 % yield). For sterically hindered substrates **13** and **15**, higher reaction temperatures were

required for high conversions, resulting in decreased selectivities (55 % *ee* and 64 % *ee*, respectively). The smaller five-membered ring substrate **17** was also allylated in moderate selectivity (70 % *ee*, 69 % yield). As shown in entry 6, the eight-membered ring enone **19** gave superior results, with the reaction being carried out at room temperature (> 98 % *ee*, 65 % yield).^[16] The use of the more nucleophilic methallyltrimethylsilane^[17] with these substrates led to the corresponding 1,4-addition products with lower enantioselectivities (< 50 % *ee*) even with slow addition of the nucleophile. Presumably, the decrease in selectivity is due to a competitive, non-catalyzed background reaction with this more reactive nucleophile.

As illustrated in Scheme 2, the optically enriched allylated products offer functionalities that can be transformed into a



Scheme 2. Representative functionalizations of allylated products.

variety of synthetically useful building blocks. For example, the methyl ester can be readily decarboxylated by using Krapcho's method (**3**→**21**).^[18] Likewise, enolization and alkylation of the allylated product **3**, followed by ring-closing metathesis (RCM) with ruthenium alkylidene **22**,^[19] and decarboxylation generates the decalin system **23**. Through the use of different ring-sized starting enones, this method offers rapid entry into optically enriched bicyclic systems. In the presence of second-generation Hoveyda–Grubbs catalyst **24**, substrate **18** undergoes cross-metathesis with methylacrylate to obtain selectively the *E*-alkene (**18**→**25**). Alternatively, the ketoester functionality can be transformed into an enolphosphate group (**18**→**26**).^[20]

In conclusion, we have developed the first catalytic enantioselective Hosomi–Sakurai conjugate allylation of cyclic unsaturated ketoesters. The protocol does not require special catalysts and/or preparation of the nucleophile; Cu(OTf)₂ and the ligand are both commercially available, as well as the relatively moisture-, oxygen-, and thermally-stable allyltrimethylsilane nucleophile. Products obtained from the reaction are easily functionalized to a variety of useful building blocks for target- and diversity-oriented synthesis. Expansion of the substrate and nucleophile scope, as well as applications to natural product synthesis are currently under investigation.

Experimental Section

Representative procedure: Cu(OTf)₂ (14.1 mg, 38.9 μ mol) and ligand **2** (12.6 mg, 42.8 μ mol) were weighed into a 13 $\times$ 100 mm test tube in a glovebox. The test tube was sealed with a rubber septum and then removed from the glovebox. CH₂Cl₂ (1.65 mL) was added under N₂. The solution was stirred for 10 min at 23 °C. A solution of enone **1** (60.0 mg, 0.39 mmol) in CH₂Cl₂ (0.3 mL) was added at 23 °C, at which point the solution turned dark purple-brown. The reaction mixture was cooled to –78 °C and allyltrimethylsilane (309 μ L, 1.95 mmol) was added dropwise. The septum was wrapped with Teflon tape and the mixture was stirred at –78 °C for 45 h. The reaction was quenched with saturated aqueous NH₄Cl at –78 °C, and was then allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 1.5 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (10:1 to 5:1, hexanes/Et₂O) to yield product **3** as a pale yellow oil mixture of keto–enol tautomers (59.0 mg, 0.30 mmol, 78 % yield).

Received: February 8, 2008

Revised: March 7, 2008

Published online: May 27, 2008

Keywords: allylation · asymmetric synthesis · copper · homogeneous catalysis · Michael reaction

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