Asymmetric Allylations

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

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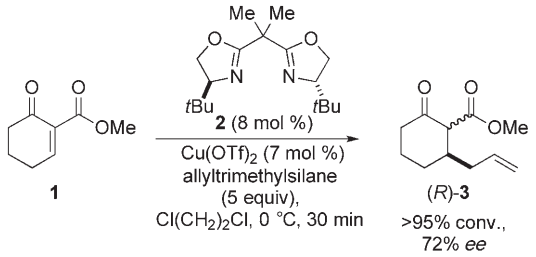
Despite impressive advances over the years,[1] there are still important transformations that lack catalytic asymmetric variants. While Lewis acid catalyzed additions of allylsilanes to carbonyl compounds[2] and acetals[3] have been well studied using catalytic,[4] as well as auxiliary-based methods 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.

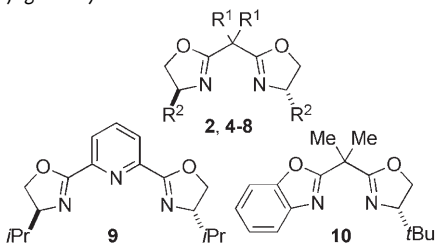
Our initial studies into the development of a chiral Lewis acid catalyst indicated that simple cyclic and acyclic α,β-unsaturated carbonyls (ketones and esters) did not react with a variety of metal–ligand combinations.[8] We therefore sought to activate the substrate by installation of a second electron-withdrawing/chelating 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 $Cl(CH_2)_2Cl$, 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 (CH_2Cl_2, Et_2O, 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. [%]	*ee* [%]
1	**4**	H	*t*Bu	>95	11
2	**2**	CH_3	*t*Bu	>95	72
3	**5**	$-(CH_2)_2-$	*t*Bu	>95	70
4	**6**	$-(CH_2)_3-$	*t*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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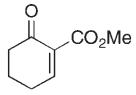
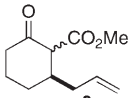
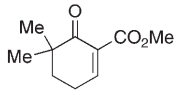
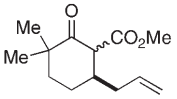
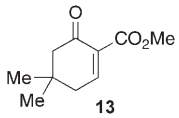
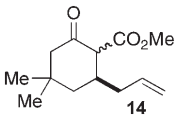
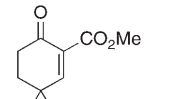
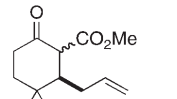
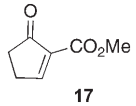
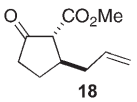
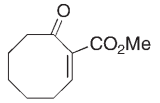
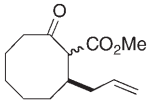
rings were introduced, such as in oxalate- and phthalic acid-derived ligands; however, these ligands did not lead to improved results compared to ligand **2**.[9] In addition, we also investigated the effect of additives upon the reaction.[15] Various desiccants (e.g., molecular sieves, $MgSO_4$), as 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 CH_2Cl_2, thus allowing for lower reaction temperatures. When run at −78 °C in CH_2Cl_2, 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).

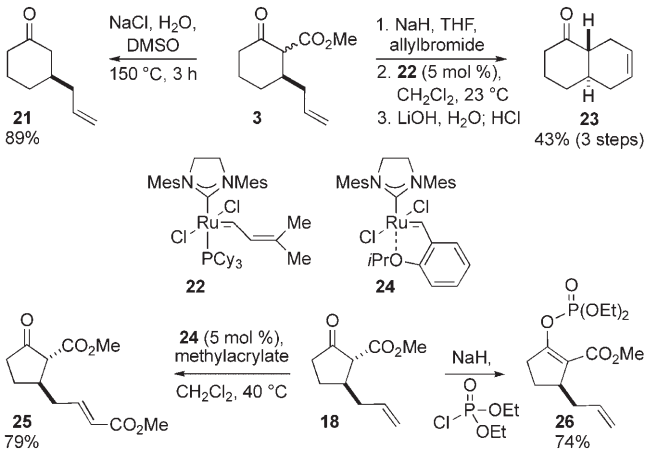
Table 2: Copper-catalyzed enantioselective Hosomi–Sakurai conjugate allyation of unsaturated ketoesters.[a]

Entry	Enone	Product	*t* [h] (*T* [°C])	Yield [%][a]	*ee* [%][b]
1[d]	 **1**	 **3**	45 (−78)	78	90
2[e]	 **11**	 **12**	48 (−50)	65	97
3[f]	 **13**	 **14**	15 (0)	51	55
4[f]	 **15**	 **16**	38 (23)	77[c]	64
5[g]	 **17**	 **18**	15 (−78)	69	70
6[d]	 **19**	 **20**	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 CH_2Cl_2, N_2. [e] CH_2Cl_2/$Cl(CH_2)_2Cl$ (5:1) as solvent. [f] $Cl(CH_2)_2Cl$ 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 μmol) and ligand **2** (12.6 mg, 42.8 μmol) were weighed into a 13 × 100 mm test tube in a glovebox. The test tube was sealed with a rubber septum and then removed from the glovebox. CH_2Cl_2 (1.65 mL) was added under N_2. The solution was stirred for 10 min at 23 °C. A solution of enone **1** (60.0 mg, 0.39 mmol) in CH_2Cl_2 (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 μL, 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 NH_4Cl at −78 °C, and was then allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.5 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (10:1 to 5:1, hexanes/Et_2O) to yield product **3** as a pale yellow oil mixture of keto–enol tautomers (59.0 mg, 0.30 mmol, 78% yield).

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