ORGANIC LETTERS

2013
Vol. 15, No. 4
768–771

Catalytic Asymmetric [4 + 2] Cycloadditions and Hosomi–Sakurai Reactions of α-Alkylidene β-Keto Imides

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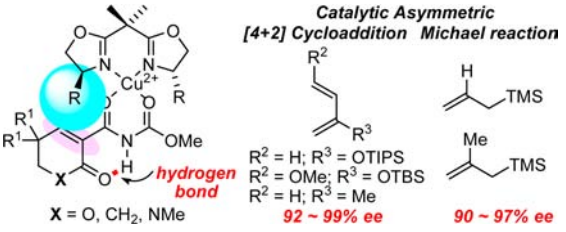
Received December 12, 2012

ABSTRACT



Highly enantioselective catalytic asymmetric reactions of rationally designed α-alkylidene β-keto imides are described. The [4 + 2] cycloadditions and Hosomi–Sakurai reactions of α-alkylidene β-keto imides proceed with high enantioselectivity and yield. The [4 + 2] cycloadditions of the imides with various dienes afford products bearing an all-carbon quaternary stereogenic center at the ring junction. α-Alkylidene β-keto imides should be useful for the enantioselective total synthesis of natural products and other catalytic asymmetric applications.

α-Alkylidene β-keto esters are reactive electrophiles capable of forming bicyclic compounds containing an all-carbon quaternary stereogenic center via cycloadditions and Michael reactions. Hence, α-alkylidene β-keto esters have been utilized in the total synthesis of natural products, e.g., oubain,[1a] drimane-type sesquiterpenoids,[1e] and others.[1] However, successful Lewis acid catalyzed asymmetric reactions of α-alkylidene β-keto esters have been limited thus far,[2−4] probably because the complex formed with a chiral Lewis acid has the disadvantage of poor enantioselection. That is, in complex **A** (Figure 1), which is a square-planar complex formed by the α-alkylidene β-keto ester and a bisoxazoline-Cu(II) catalyst,[5] the alkene would be located far from the bisoxazoline substituent, resulting in low enantioselectivity.[6] On the other hand, *N*-acryloyloxazolidin-2-one[7] and its derivatives have been used in many catalytic asymmetric reactions[8] because, in complex **B** (Figure.1), the bisoxazoline substituent effectively shields one side of the s-*cis* alkene.[5]

(1) For recent examples, see: (a) Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1272. (b) Hsieh, M.-T.; Liu, H.-J.; Ly, T. W.; Shia, K.-S. *Org. Biomol. Chem.* **2009**, *7*, 3285. (c) Li, W.; Liu, X.; Zhou, X.; Lee, C.-S. *Org. Lett.* **2010**, *12*, 548. (d) De Lorbe, J. E.; Lotz, M. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 1576. (e) Shi, H.; Fang, L.-C.; Tan, C.-H.; Shi, L.-L.; Zhang, W.-B.; Li, C.-C.; Luo, T.-P.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944.

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(4) For the recent use of α-alkylidene β-keto esters in asymmetric catalysis, see: Schotes, C.; Mezzetti, A. *ACS Catal.* **2012**, *2*, 528.

(5) Strictly speaking, the bisoxazoline–Cu(II) complex may have a distorted square-planar geometry. See: (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

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10.1021/ol303381c
Published on Web 01/31/2013

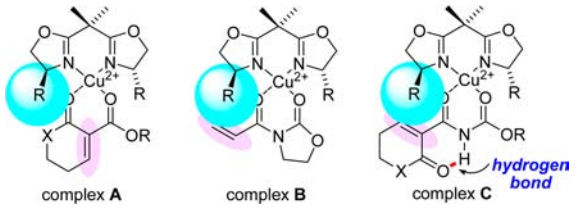


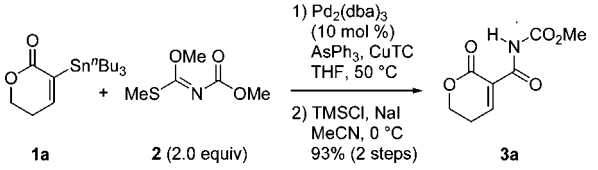
Figure 1. Proposed structures of complexes formed by a bisoxazoline-Cu(II) catalyst with an α-alkylidene β-keto ester (complex **A**), *N*-acryloyl oxazolidin-2-one (complex **B**), and an α-alkylidene β-keto imide (complex **C**: X = CH_2, NMe, O).

α-Alkylidene β-keto imides are attractive compounds because the acidic imide hydrogen can form an internal hydrogen bond to restrict free rotation of the imide (Figure 1). As a result, reactions via complex **C** are expected to show high enantioselectivity because the alkene would be located at the same position as that in complex **B**.

The chief concern in the reaction via complex **C** was whether the weak hydrogen bonding would be retained during the reaction. However, the hydrogen-bond-directed stereoselective reactions[9] are known and, moreover, asymmetric organocatalysis utilizing hydrogen bonding has recently been reported.[10] In addition, since imides can be transformed into a variety of functional groups,[10,11] products of the reactions of α-alkylidene β-keto imides would be useful synthetic intermediates. Therefore, we investigated catalytic asymmetric reactions of α-alkylidene β-keto imides and report herein their highly enantioselective catalytic asymmetric [4 + 2] cycloadditions and Hosomi−Sakurai reactions.

α-Alkylidene β-keto imides were hardly accessible by known methods owing to their sensitivity toward basic conditions.[12] However, we found that the palladium-catalyzed coupling reaction[13] of organostannane **1a** with methyl *N*-[methoxy(methylthio)methylene]carbamate **2**[14] afforded the corresponding imino ether, which was converted to α-alkylidene β-keto imide **3a** in 93% yield over two steps (Scheme 1). This method was successfully applied for the preparation of **3b**−**d**,[15] allowing us to investigate the reactions of α-alkylidene β-keto imides.

Scheme 1. Preparation of α-Alkylidene β-Keto Imide **3a**



The catalytic asymmetric [4 + 2] cycloaddition of **3a** with **4a** was first examined (Table 1). The reaction with the **L1**[16a]−$Cu(OTf)_2$ catalyst (10 mol %) at 0 °C afforded **5aa** (71%, 77% ee, entry 1). The reactions with ligand **L2**[16b] (entry 2) and ligand **L3**[16a] (entry 3) did not improve the enantioselectivity (47% ee and 33% ee, respectively). The reaction with **L1**−$Cu(OTf)_2$ in mixed solvent **A** (CH_2Cl_2/toluene = 1:5) required 7 h for completion, but the ee was improved to 85% (entry 4). The reaction at −15 °C was slow, but the ee further increased to 90% (entry 5). Use of molecular sieves (MS 4A) as an additive improved the yield (entry 6), and finally, the reaction with ligand **L4**[16c] afforded ***ent*-5aa** in 98% yield and 97% ee (entry 7).

The [4 + 2] cycloadditions of **3a** with dienes **4b** and **4c** were also examined (Table 2). The reaction of **3a** with reactive Danishefsky's diene **4b** in the presence of **L1**−$Cu(OTf)_2$ (10 mol %) proceeded at −78 °C to afford **5ab** in 94% yield (endo/exo = 13:1) and 92% ee (entry 1). To the best of our knowledge, this result is the first example of a catalytic asymmetric [4 + 2] cycloaddition with Danishefsky's diene affording a bicyclic product containing an all-carbon quaternary stereogenic center in high ee. The reaction of **3a** and **4b** with ligand **L4** afforded **5ab** with 58% yield and 60% ee (endo/exo = 15:1, entry 2), though the reason for the low yield and ee is unknown.

The reaction of **3a** and less reactive isoprene **4c** did not proceed with **L1**−$Cu(OTf)_2$ (10 mol %) at room temperature (entry 3). In contrast, the reaction did proceed using ligand **L4** at rt to afford **3ac** (61%, 73% ee, entry 4), though 42 h were required for completion. Use of **L4**−$Cu(NTf_2)_2$ (20 mol %) reduced the reaction time to 16 h, and the yield and ee were improved to 100% and 94%, respectively (entry 5).

The [4 + 2] cycloaddition of cyclohexenone derivative **3b** and **4a** with **L4**−$Cu(OTf)_2$ (10 mol %) at −20 °C successfully afforded **5ba** (82% yield, 95% ee, Scheme 2). It was expected that the reaction of **3c** would proceed slowly owing to the steric hindrance derived from the all-carbon quaternary center adjacent to the reacting alkene.

(8) Selected references for the utility of *N*-acryloyl oxazolidin-2-one and its congeners. For 1,3-dipolar addition: (a) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836. (c) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276. For Michael addition of organozinc reagent: (d) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276.

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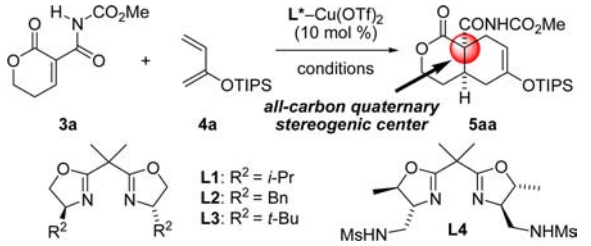
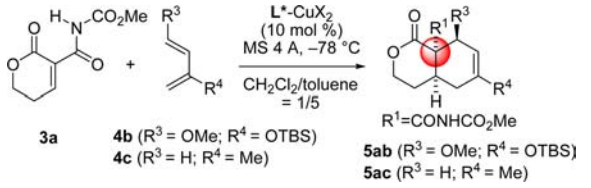
Table 1. Catalytic Asymmetric [4 + 2] Cycloaddition of **3a** with **4a**



entry	L*[a]	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c,d] (%)
1	**L1**	CH_2Cl_2	0	2.5	71	77
2	**L2**	CH_2Cl_2	0	2.5	74	47
3	**L3**	CH_2Cl_2	0	3.0	96	33
4	**L1**	**A**[e]	0	7.0	74	85
5	**L1**	**A**[e]	−15	21	70	90
6[f]	**L1**	**A**[e]	−15	19	89	91
7[f]	**L4**	**A**[e]	−15	17	**98**	**−97**[g]

[a] 10.1 mol % of ligand was used. [b] Isolated yields. [c] For HPLC conditions, see Supporting Information (SI). [d] The absolute structure was proposed based on the X-ray structure of **5db**. [e] **A**: CH_2Cl_2/toluene = 1:5. [f] MS 4 A was added. [g] A minus sign "−" means reversal of the enantioselectivity.

Table 2. Catalytic Asymmetric [4 + 2] Cycloaddition of **3a** with **4b** or **4c**



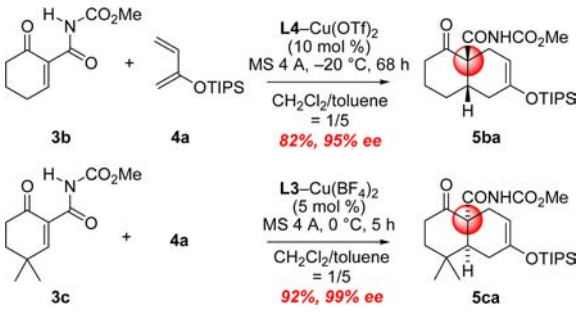
entry	4	L*[a]	X	temp (°C)	time (h)	yield (%)[b]	ee[c,d] (%)
1	**4b**	**L1**	OTf	−78	2	**94 (13/1)**[e]	**92**
2	**4b**	**L4**	OTf	−78	3	58 (15/1)[e]	−60[f]
3	**4c**	**L1**	OTf	rt	12	0	–
4	**4c**	**L4**	OTf	rt	42	61	−73[f]
5[g]	**4c**	**L4**	NTf_2	rt	16	**100**	**−94**[f]

[a] 10.1 mol % of ligand was used. [b] Isolated yields. [c] For HPLC conditions, see SI. [d] The absolute structure was proposed based on the X-ray structure of **5db**. [e] The *endo*/*exo* (*endo* isomer is shown above) ratio of **5ab** is shown in parentheses. [f] A minus sign "−" means reversal of the enantioselectivity. [g] $Cu(NTf_2)_2$ (20 mol %) and ligand (20.2 mol %) were used.

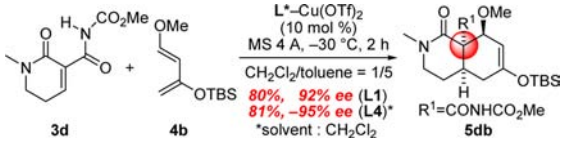
Interestingly, the reaction of **3c** and **4a** with **L3**−$Cu(BF_4)_2$ (5 mol %) at 0 °C was completed after 5 h with 92% yield and 99% ee, indicating the good reactivity of **3c** or **L3**−$Cu(BF_4)_2$.

The **L1**−$Cu(OTf)_2$-catalyzed [4 + 2] cycloaddition of α,β-unsaturated lactam **3d** with **4b** proceeded at −30 °C to afford **5db** (80%, 92% ee), which is a core structure of manzamine A,[17] and the reaction with **L4** gave better results (81%, 95% ee) (Scheme 3).

Scheme 2. Catalytic Asymmetric [4 + 2] Cycloaddition of **3b** and **3c** with **4a**



Scheme 3. Catalytic Asymmetric [4 + 2] Cycloaddition of **3d** and **4b**



The Lewis acid catalyzed asymmetric Hosomi−Sakurai reactions[18] of imides **3a** and **3b** with allyltrimethylsilane **6a** and methallyltrimethylsilane **6b** were also examined (Table 3). To the best of our knowledge, only one study on the Lewis acid catalyzed asymmetric Hosomi−Sakurai reaction using **6a** has been reported.[18b] The reaction of **3a** with **6a** in the presence of **L1**−$Cu(OTf)_2$ (10 mol %) was very slow at rt. However, the reaction with **L4**−$Cu(OTf)_2$ (10 mol %) at rt afforded **7aa** in 87% yield with 82% ee (entry 1, Table 3). The same reaction at 0 °C was sluggish, but use of 20 mol % of the catalyst resulted in a 94% yield and 92% ee (entry 2). The reaction of **3a** with more reactive **6b**[19] went to completion even at −30 °C to afford **7ab** in 95% yield with 92% ee (entry 3). Like the reaction of **3a**, the reaction of **3b** with **6a** using **L1**−$Cu(OTf)_2$ (10 mol %) proceeded slowly at rt, giving **7ba** in 68% yield with 50% ee (entry 4). The use of more acidic **L4**−$Cu(OTf)_2$ (10 mol %) improved the yield and ee (88%, 88% ee, entry 5), but the same reaction at 0 °C was sluggish, though the ee was improved to 90% (entry 6). Finally, the reaction using 20 mol % of **L4**−$Cu(OTf)_2$ at 0 °C was found to afford **7ba** in 80% yield with 90% ee (entry 7). The reaction of **3b** with **6b** using **L1**−$Cu(OTf)_2$ (10 mol %) proceeded at −30 °C to afford **7bb** in 93% yield, but the ee was only 77% (entry 8).

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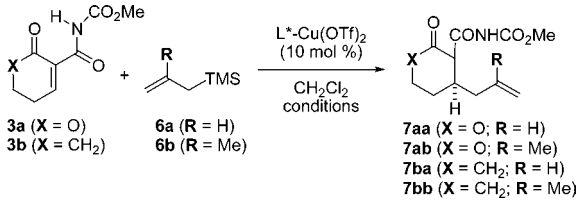
(18) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049. The authors mention that the reactions with methallyltrimethylsilane afforded products with less than 50% ee.

(19) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(20) See SI for the details.

Table 3. Catalytic Asymmetric Hosomi–Sakurai Reaction of **3** and **6**



entry	**3**	**6**	**L*** [a]	temp (°C)	time (h)	yield (%) [b]	ee (%) [c,d]
1	**3a**	**6a**	**L4**	rt	22	87 [e]	−82
2 [f]	**3a**	**6a**	**L4**	0	36	**94** [e]	**−92**
3	**3a**	**6b**	**L4**	−30	7.5	**95** [e]	**−92**
4	**3b**	**6a**	**L1**	rt	20	68	50
5	**3b**	**6a**	**L4**	rt	24	88	−88
6	**3b**	**6a**	**L4**	0	71	39	−90
7 [f]	**3b**	**6a**	**L4**	0	47	**80**	**−90**
8	**3b**	**6b**	**L1**	−30	36	93	77
9	**3b**	**6b**	**L4**	−30	10.5	**90**	**−97**

[a] 10.1 mol % of ligand was used. [b] Isolated yields. [c] For HPLC conditions, see SI. [d] The absolute structure was proposed based on the X-ray structure of **5db**. [e] Yield after treatment of the initial products with TBAF. See SI for the details. [f] 20 mol % of **L4**–$Cu(OTf)_2$ catalyst was used.

However, the same reaction with **L4**–$Cu(OTf)_2$ (10 mol %) gratifyingly gave better results (90%, 97% ee, entry 9). As summarized above, **L4**–$Cu(OTf)_2$ was found to be suitable for the catalytic asymmetric Hosomi–Sakurai reactions of **3**.

The crystal structure of **3d** (Figure 2a) has a planar π-conjugated system, and the imide NH bond is oriented toward the carbonyl oxygen of the lactam. The ^{1}H NMR spectrum of **3d** showed the downfield shift of the imide NH signal, which appeared around 11 ppm, suggesting the presence of the hydrogen bond. The absolute structure of **5db** was also confirmed by X-ray crystallographic analysis (Figure 2b), which suggests that the [4 + 2] cycloaddition of **3d** proceeded at the less hindered side of the dienophile in complex **C** (Figure 1). The ^{1}H NMR spectra of imides **3a**–**3d** suggest the presence of the H-bonded imide NH. Hence, we speculated that all the reactions of **3a**–**3d** would proceed at the less-hindered side of the alkene in complex **C**. These results indicate that the internal H-bond in **3** was retained during the reactions, even those with the catalyst formed by ligand **L4** and the Cu(II) reagent, which was proposed to have a H-bond between the counteranion and the ligand.[16c]

In summary, we demonstrated the utility of rationally designed α-alkylidene β-keto imides for Lewis acid catalyzed asymmetric reactions. The catalytic asymmetric [4 + 2] cycloadditions of α-alkylidene β-keto imides afford products bearing an all-carbon quaternary stereogenic center at the ring junction with high yield and ee. The imide groups in the products could be convertible to different functional groups. For example, compounds **7ba** and **7bb** were easily transformed to the corresponding methyl esters in 83% and 81% yields, respectively.[20] Hence, the products obtained by catalytic asymmetric reactions of α-alkylidene β-keto imides would be useful for the enantioselective total synthesis of natural products. Moreover, Hosomi–Sakurai reactions of α-alkylidene β-keto imides, which are different types of reactions when compared with [4 + 2] cycloaddition, give products with high yield and ee as well, suggesting the versatile utility of α-alkylidene β-keto imides in asymmetric catalysis. Consequently, further studies on asymmetric catalysis utilizing α-alkylidene β-keto imides are now underway and will be reported in due course.

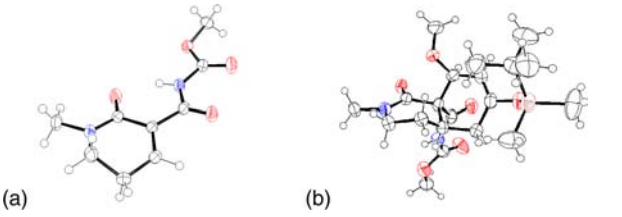


Figure 2. X-ray crystal structures of (a) **3d** and (b) **5db**.

Acknowledgment. This work was financially supported in part by The Grant-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis based on Reaction Integration. Development of New Methods and Creation of New Substances" (No. 2105).

Note Added after ASAP Publication. Scheme 3 contained errors in the version published ASAP on January 31, 2012; the correct version reposted February 15, 2013.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.