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Cu(I)-Catalyzed Hetero-Diels−Alder Reaction between Danishefsky-Type Siloxy Dienes and Ketones

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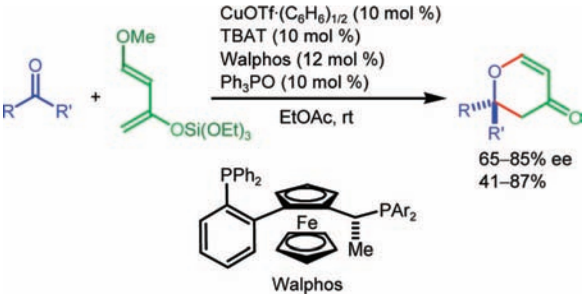
ABSTRACT



A general catalytic method for the hetero-Diels−Alder reaction between Danishefsky-type siloxy dienes and ketones was developed. Optimum results were produced with a catalyst generated from CuOTf·(C$_6$H$_6$)$_{1/2}$ and TBAT with Ph$_3$PO as the catalytic additive. This reaction was extended to an asymmetric variant, using a Cu(I)−Walphos catalyst.

Catalytic asymmetric construction of molecules containing tetrasubstituted carbons is a critical challenge in organic synthesis.[1] Such molecules can be unique and useful pharmaceutical leads in medicinal chemistry.[2] Dihydropyranones are versatile components of various biologically active compounds.[3] One of the most direct methods for the synthesis of dihydropyranones is the hetero-Diels−Alder reaction between the Danishefsky's diene or its derivatives and carbonyl-containing compounds.[4] Catalytic asymmetric hetero-Diels−Alder reactions to produce enantiomerically enriched dihydropyranones are currently limited, however, to the use of aldehydes[5] and α-ketoesters[6] as dienophiles.[7] The corresponding reaction of simple ketones has yet to be developed because the reactivity of ketones is attenuated compared with that of aldehydes and α-ketoesters. Herein, we report the first entry in this category using Cu(I) catalysis.

Although there are some reports of racemic hetero-Diels−Alder reactions of ketones,[8] their substrate generality

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[1] (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I. *Tetrahedron* **2003**, *59*, 10105. (e) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284. (f) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (g) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (h) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (i) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647.

[2] For examples, see: (a) Pommier, Y.; Kohlhagen, G.; Kohn, K. W.; Leteurtre, F.; Wani, M. C.; Wall, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 8861 (camptothecins). (b) Como, J. A.; Dismukes, W. J. *New Engl. J. Med.* **1994**, *330*, 263 (triazole antifungals).

[3] For example, see: Li, H.; Tatlock, J.; Linton, A.; Gonzalez, J.; Borchardt, A.; Dragovich, P.; Jewell, T.; Prins, T.; Zhou, R.; Blazel, J.; Parge, H.; Love, R.; Hickey, M.; Doan, C.; Shi, S.; Duggal, R.; Lewisc, C.; Fuhrman, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4834 (HCV RNA polymerase inhibitors).

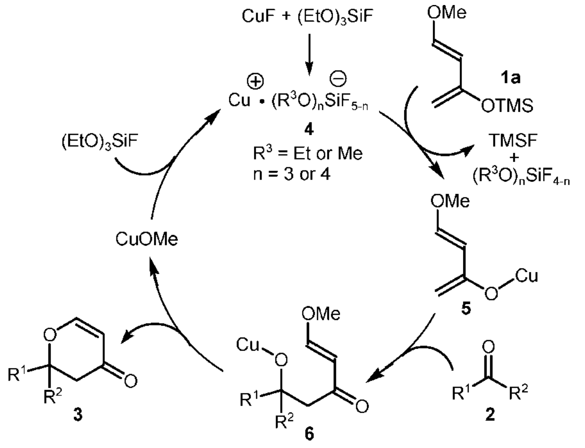
[4] For reviews of hetero-Diels−Alder reactions, see: (a) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (c) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (d) Gouverneur, V.; Reiter, M. *Chem. Eur. J.* **2005**, *11*, 5806. (e) Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147.

[5] For examples, see: (a) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366, and references cited therein. (b) Yang, X.-B.; Feng, J.; Zhang, J.; Wang, N.; Wang, L.; Liu, J.-L.; Yu, X.-Q. *Org. Lett.* **2008**, *10*, 1299. (c) Du, H.; Zhang, X.; Wang, Z.; Bao, H.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2008**, 2248, and references cited therein.

10.1021/ol802134a CCC: $40.75

is not satisfactory. Prior to this report, the most successful example of this has been Rawal's reaction using 1-amino-3-siloxybutadiene (Rawal's diene) through hydrogen-bonding activation of ketones with protic solvents.[8a] Although the use of reactive cyclic ketones in these reactions produces high yields (up to 85%), aliphatic ketones produce only moderate yields (33−44%), and the use of aromatic ketones has not been described. Therefore, the development of catalytic hetero-Diels−Alder reaction of ketones with a synthetically useful substrate scope is very challenging.

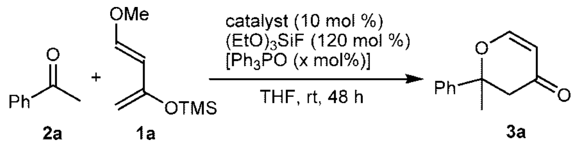
Scheme 1. Hypothesized Catalytic Cycle of Copper(I)-Catalyzed Hetero-Diels−Alder Reaction



Our initial plan to realize the catalytic hetero-Diels−Alder reaction between the Danishefsky's diene (**1a**)[9] and ketones was based on the previous development of a CuF-catalyzed aldol reaction to ketones.[10] In this aldol reaction, various ketones and ketene silyl acetals were reacted in the presence of a $CuF\cdot 3PPh_3\cdot 2EtOH$ catalyst (2.5 mol %) and a stoichiometric amount of $(EtO)_3SiF$. High reactivity was attributed to the generation of highly nucleophilic copper enolates through transmetalation of the silyl enolates.[11] $(EtO)_3SiF$ efficiently trapped the intermediate copper aldolate, facilitating the turnover-limiting catalyst regeneration step. We hypothesized that the Danishefsky's diene (**1a**) would be activated by a CuF catalyst [existing as copper silicate **4** in the presence of $(EtO)_3SiF$] through transmetalation, similar to ketene silyl acetals, generating the corresponding copper enolate **5** (Scheme 1). The copper enolate should be reactive enough, and the addition to ketones **2** would be possible. The resulting copper aldolate **6** would be expected to cyclize via a sequential conjugate addition followed by the elimination of copper methoxide. Finally, catalytically active copper silicate **4** would be regenerated by trapping copper methoxide with $(EtO)_3SiF$.

On the basis of this hypothesis, we first applied the optimized conditions of the aldol reaction to ketones [$CuF\cdot 3PPh_3\cdot 2EtOH$ complex as a catalyst (10 mol %) in the presence of $(EtO)_3SiF$ (120 mol %)] to the hetero-Diels−Alder reaction between acetophenone (**2a**) and siloxy diene **1a** at room temperature.[12] The desired cyclized product **3a** was obtained in 24% yield (Table 1, entry 1). The addition of tol-BINAP (20 mol %) slightly improved the yield (43%: entry 2). To further improve these promising results, we screened catalytic combinations of a $CuOTf\cdot(C_6H_6)_{1/2}$−racemic BINAP complex and several fluoride sources, expecting that the CuF−BINAP complex would be generated in situ. The reaction did not proceed with the use of CsF or NaF as the fluoride source (entries 3 and 4), but the yield of **3a** markedly improved to 70% with the use of TBAT (tetrabutylammonium difluorotriphenylsilicate)[13] (entry 5).[14] Copper triflate

Table 1. Optimization of Reaction Conditions



entry	catalyst	Ph_3PO (mol %)	yield (%)[a]
1	$CuF\cdot 3PPh_3\cdot 2EtOH$	0	24
2	$CuF\cdot 3PPh_3\cdot 2EtOH$ + tol-BINAP[b]	0	43
3	CuOTf[c] + CsF + *rac*-BINAP[d]	0	0
4	CuOTf[c] + NaF + *rac*-BINAP[d]	0	0
5	CuOTf[c] + TBAT + *rac*-BINAP[d]	0	70
6	CuOTf[c] + TBAT + *rac*-BINAP[d]	10	77
7[e]	CuOTf[c] + TBAT + *rac*-BINAP[d]	10	8

[a] Isolated yield. [b] 20 mol % of tol-BINAP was added. [c] $CuOTf\cdot(C_6H_6)_{1/2}$. [d] 12 mol % of racemic BINAP was added. [e] In the absence of $(EtO)_3SiF$.

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(6) (a) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. (b) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231. (c) Dalko, P. I.; Moisan, L.; Cossy, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 625. (d) Furuno, H.; Kambara, T.; Tanaka, Y.; Hanamoto, T.; Kagawa, T.; Inanaga, J. *Tetrahedron Lett.* **2003**, *44*, 6129. (e) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (f) Akullian, L. C.; Snapper, M. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532. (g) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240.

(7) For a racemic example using ketones, see: Liu, J.; Li, X.; Wang, J.; Feng, X. *Adv. Synth. Catal.* **2006**, *348*, 939.

(8) (a) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. (b) Kitazawa, T.; Mukaiyama, T. *Heterocycles* **2006**, *69*, 417. (c) Guay, V.; Brassard, P. *Tetrahedron* **1984**, *40*, 5039.

(9) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(10) (a) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644. (b) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

(11) For pioneering studies on transmetalation from a silyl enolate to a copper enolate, see: Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124.

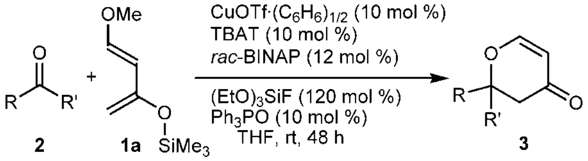
(12) No reaction proceeded with $Cu(OTf)_2$ or CuF_2 catalyst.

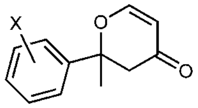
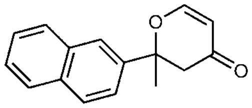
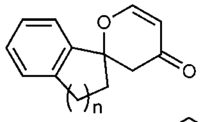
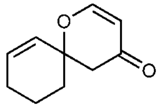
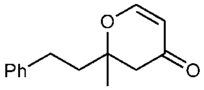
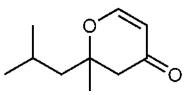
(13) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

(14) The results of Table 1, entries 2−5, suggest that the tetrabutylammonium cation facilitates the catalytic cycle. The fact that **3a** was obtained in 90% yield with $CuF\cdot 3PPh_3\cdot 2EtOH$−tol-BINAP catalyst (10 mol %) in the presence of 30 mol % of $Bu_4N\cdot BF_4$ (cf. 43% yield in the absence of $Bu_4N\cdot BF_4$, Table 1, entry 2) supports this consideration. We assume that the tetrabutylammonium cation facilitates the catalyst regeneration step from intermediate **6** via ion exchange. See the Supporting Information for detailed discussion.

could not be replaced by copper(I) chloride, copper(I) iodide, or copper(I) acetate. Racemic BINAP was the most suitable ligand, and other phosphines such as dppe, dppf, and xantphos produced much less satisfactory results (less than 5% yield). Finally, the yield and reaction rate were improved further in the presence of a Lewis basic triphenylphosphine oxide as an additive (entry 6).[15] Notably, on the basis of NMR and TLC analysis, aldol intermediate (silylated **6**) was not detected in the reaction mixture, and cyclized **3a** was the major product even before adding aqueous HCl to quench the reaction. Consistent with the observation in the previous aldol reaction to ketones,[10] there was no catalyst turnover in the absence of (EtO)$_3$SiF (entry 7).

Table 2. Substrate Scope of Cu(I)-Catalyzed Hetero-Diels−Alder Reaction of Ketones



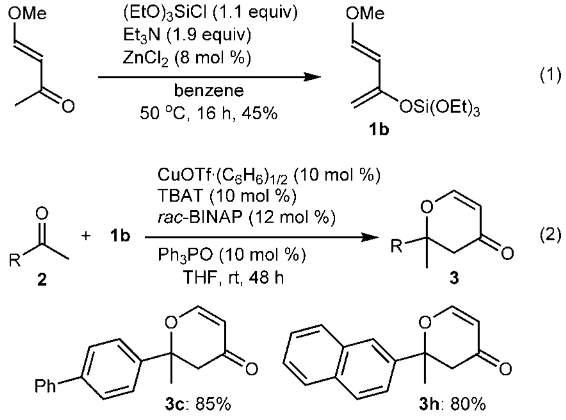
entry	products			yield (%)[a]
1		X = H	(**3a**)	77
2		X = 4-Me	(**3b**)	81
3		X = 4-Ph	(**3c**)	88
4		X = 4-vinyl	(**3d**)	80
5		X = 4-F	(**3e**)	80
6		X = 4-Br	(**3f**)	85
7		X = 3-Br	(**3g**)	75
8			(**3h**)	90
9		n = 1	(**3i**)	85
10		n = 2	(**3j**)	87
11			(**3k**)	85
12			(**3l**)	72
13			(**3m**)	70

[a] Isolated yield.

Under the optimized conditions, we investigated the substrate scope of the catalytic hetero-Diels−Alder reaction (Table 2). Various aromatic ketones generally produced high chemical yields (entries 1−10). Specifically, styrene ketone **2d**, which polymerized under acidic conditions, was tolerated (entry 4). Unique spiro-products **3i**, **3j**, and **3k** were obtained in high yields with the use of unsymmetrical cyclic ketones (entries 9−11). In the reaction of cyclohexenone **2k**, hetero-Diels−Alder product **3k** was produced exclusively and no detectable amounts of the Diels−Alder product were generated (entry 11). Aliphatic ketones were also competent substrates, affording the products in synthetically useful yields (entries 12 and 13).

At this stage, a general catalytic hetero-Diels−Alder reaction of ketones was developed, but the consumption of a stoichiometric amount of silyl fluoride was unsatisfactory with regard to atom economy.[16] On the basis of the hypothetical catalytic cycle shown in Scheme 1, we expected that if the triethoxysilyl version of the Danishefsky's diene (**1b**) was used, (EtO)$_3$SiF would be generated at the initial transmetalation step, instead of TMSF (from **4** to **5** in Scheme 1). The generated (EtO)$_3$SiF should then act as a CuOMe trapping reagent in the catalyst regeneration step. A more atom-economical catalytic system could thus be constructed without forming a stoichiometric amount of waste TMSF. Triethoxysiloxy diene **1b** was prepared on a gram scale by using the same procedure as that for Danishefsky's diene **1a**[9] (Scheme 2, eq 1).

Scheme 2. Synthesis of Triethoxysiloxy Diene **1b** (Eq 1) and Simplified Catalytic Hetero-Diels−Alder Reaction of Ketones Using **1b** (Eq 2)



Representative results using the new diene **1b** in the absence of the (EtO)$_3$SiF additive are summarized in Scheme 2, eq 2. Comparable results were obtained with ketones **2c** and **2h** under the conditions described in Table 2. Therefore, a stoichiometric amount of (EtO)$_3$SiF was not required to

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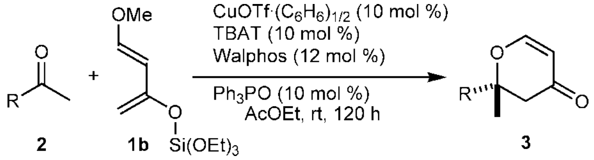
(15) Triphenylphosphine oxide would coordinate to the silicon atom and generate a pentacoordinated silicon. This species is more Lewis acidic than the original tetracoordinated silicon (for a leading reference, see: Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D *J. Am. Chem. Soc.* **2005**, *127*, 3774.), and should readily accept the counterion (fluoride or alkoxide) of copper. Because copper silicate formation is the initiating step of transmetalation between silicon and copper, formation of a pentacoordinated silicon would facilitate the active copper enolate formation from **1a** and **1b**. See the Supporting Information for details.

(16) Trost, B. M. *Science* **1991**, *254*, 1471.

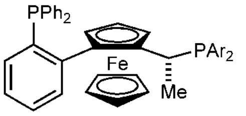
maintain reactivity under these simplified and more atom-economical conditions.

This method was next extended to the catalytic enantioselective hetero-Diels−Alder reaction of ketones. Screening of chiral phosphines[17] led us to identify Walphos-type diphosphines as the optimized chiral ligand (Table 3).[18] The use of ethyl acetate as the solvent afforded better enantioselectivity than THF. High to moderate enantioselectivity was obtained from aromatic ketones. Unfortunately, aliphatic ketones produced unsatisfactory results (no reaction or less than 10% ee) under the catalytic asymmetric conditions. Although the substrate generality and enantioselectivity were not quite satisfactory, to our knowledge, this is the first example of a catalytic enantioselective hetero-Diels−Alder reaction of ketones reported to date. The synthesis of **3** in an enantiomerically enriched form using alternative synthetic methodologies is not simple. The absolute configuration of the products was determined to be (*R*) by conversion to a known compound[17] and by X-ray crystallography (Figure 1).[19]

Table 3. Substrate Scope of Cu(I)-Catalyzed Asymmetric Hetero-Diels−Alder Reaction of Ketones



entry	product	ligand	yield (%)[a]	ee (%)[b]
1	**3a**	**8**	80	85[c]
2	**3b**	**8**	67	78[c]
3	**3c**	**7**	87	76
4	**3d**	**7**	80	74
5	**3e**	**7**	87	70
6	**3h**	**7**	84	70
7	**3j**	**7**	41	65



Walphos
7 : Ar = Ph
8 : Ar = 3,5-$(CF_3)_2C_6H_3$

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] The absolute configuration of the products was determined to be (*R*).

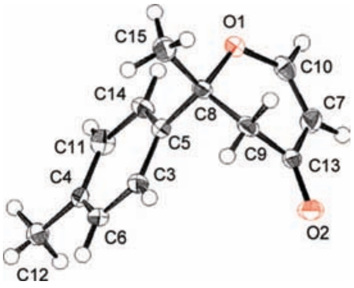


Figure 1. X-ray crystallography of compound **3b**.

In summary, we developed a general catalytic method for a hetero-Diels−Alder reaction between Danishefsky-type siloxy dienes and ketones. A Cu(I) catalyst generated from CuOTf and TBAT produced the highest activity. Due to the development of new triethoxysiloxy diene **1b**, only a catalytic amount of the fluoride source was required. This method was extended to the first catalytic asymmetric hetero-Diels−Alder reaction of ketones using chiral Cu(I)−Walphos complexes. Futher studies to improve the enantioselectivity and substrate generality, as well as detailed mechanistic studies, are ongoing.

Acknowledgment. Financial support was provided by Grant-in-Aid for Scientific Research (S) and (B) from JSPS, and that for Priority Areas "Chemistry of Concerto Catalysis" from MEXT.

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

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(17) See the Supporting Information for details.

(18) Using **1a** and a stoichiometric amount of $(EtO)_3SiF$ produced comparable yields and enantioselectivities to the simplified method with **1b** shown in Table 3. The observed comparable enantioselectivities between the two methods strongly support that the actual active species is the identical copper enolate, which is generated through transmetalation of the siloxy dienes.

(19) Interestingly, the aryl group, which is bulkier than the methyl group, exists at the axial position in this crystal structure.