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Enantioselective Total Synthesis of Erogorgiaene: Applications of Asymmetric Cu-Catalyzed Conjugate Additions of Alkylzincs to Acyclic Enones

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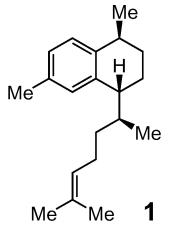
Abstract: The first enantioselective synthesis of erogorgiaene (**1**), an inhibitor of mycobacterium tuberculosis, is disclosed. The total synthesis highlights the utility of asymmetric conjugate additions (ACA) of alkylzincs to acyclic α,β-unsaturated ketones catalyzed by peptidic phosphine ligands and $(CuOTf)_2 \cdot C_6H_6$. Moreover, several critical attributes of this catalytic C−C bond-forming reaction are illustrated in the context of the total synthesis; these include the significance of various structural features of the amino acid-based chiral ligands and the chiral ligand's effectiveness in reactions involving achiral and chiral substrates. In addition, the total synthesis showcases some of the special properties of nonphosphine Ru complex **3** as a highly effective catalyst for olefin cross-metathesis.

Introduction

During the past several years, efforts in these laboratories have been focused on the discovery and development of new catalytic enantioselective C−C bond-forming reactions.[1] A critical aspect of these investigations has been to utilize such asymmetric methods in the total syntheses of biologically active molecules.[2] Through these studies, we explore the utility and determine the limitations of different processes, as well as identify ways in which various catalytic protocols can be used sequentially[3] to access a target molecule efficiently.[4]

It was in this context that we set out to develop an efficient route for the enantioselective total synthesis of antimycobacterial agent erogorgiaene **1**.[5] Our synthesis strategy was devised so



1

erogorgiaene

that it would benefit from the unique ability of amino acid-based chiral phosphine ligands, such as **2**, to effect Cu-catalyzed asymmetric conjugate additions (ACA) of alkylzincs to acyclic enones.[6,7] Thus, in the course of this study we demonstrate that (i) Cu-catalyzed ACA can be carried out reliably on multigram scale to obtain the desired acyclic β-alkylcarbonyls in high yield and with excellent enantioselectivity and (ii) Cu-catalyzed ACA can be used to control relative stereochemistry in instances

(1) (a) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284. (b) Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 431−454. (c) Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 991−1016. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.

(2) For example, see: (a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302−10316. (b) Johannes, C. W.; Visser, M. S.; Weatherhead G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340−8347. (c) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691. (d) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032−9034.

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(4) For examples of enantioselective total syntheses where catalytic reactions play a prominent role, see: (a) Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871−1872. (b) Fox, M. E.; Li, C.; Mariano, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467−5480. (c) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624−9625. For a review on the utility of catalytic enantioselective reactions in target oriented synthesis, see: (d) Hoveyda, A. H. In *Stimulating Concepts in Chemistry*; Vogtle, F., Fraser Stoddart, J., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 145−162.

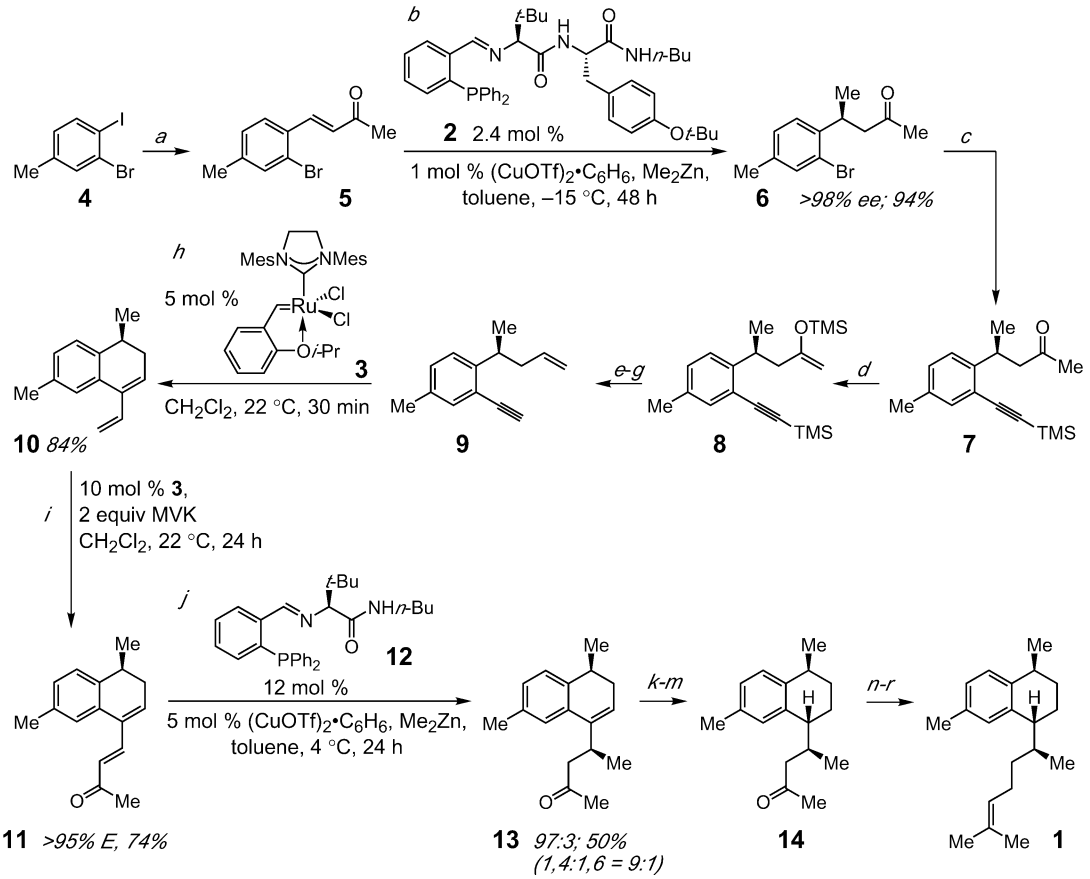
(5) Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100−102.

(6) (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (b) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. For related transformations involving cyclic substrates, see: (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (d) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (e) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363.

(7) The uniqueness of amino acid-based ligands such as **2** (refs 6a,b) is tied to the fact that the large majority of Cu-catalyzed asymmetric conjugate additions of alkylmetals to enones involve cyclic systems, and nearly all the reported cases regarding acyclic substrates (predominantly chalcones) relate to reactions only with Et_2Zn. For Cu-catalyzed enantioselective conjugate addition of MeMgI to an acyclic enone (<10−76% ee), see: (a) van Klaveren, M.; Lambert, F.; Eijkelkamp, J. F. M.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135−6138. For Cu-catalyzed asymmetric conjugate addition of Me_3Al to acyclic enones (80−93% ee), see: (b) Fraser, P. K.; Woodward, S. *Chem.−Eur. J.* **2003**, *9*, 776−783. For related reviews, see: (c) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171−196. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (e) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002, pp 224−258.

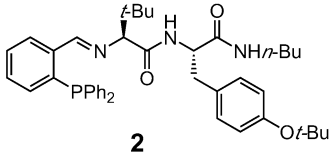
10.1021/ja0305407 CCC: $27.50

Scheme 1. Enantioselective Total Synthesis of Erogorgiaene[a]

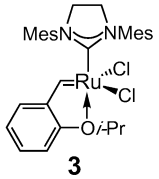


[a] (a) 5 mol % $Pd(OAc)_2$, 2 equiv $H_2C{=}C(H)COMe$, 2.5 equiv $NaHCO_3$, 1 equiv *n*-Bu_4NCl, DMF, 4 Å molecular sieves, 60 °C; 88%. (c) 5 mol % $Pd(PPh_3)_4$, 1.2 equiv $Bu_3SnCCSiMe_3$, 1 mol % BHT, toluene, 100 °C; 96%. (d) 1.25 equiv LiTMP, 1.33 equiv TMSCl, THF, −78 °C; 9:1 selectivity, 97%. (e) 1.2 equiv MeLi, THF, 0 °C; 1.2 equiv Tf_2NPh, THF, −78 °C → 4 °C; 76%. (f) 5 mol % $Pd(PPh_3)_4$, 1.2 equiv Bu_3SnH, 3 equiv LiCl, 5 mol % BHT, THF, 60 °C; 82%. (g) K_2CO_3, MeOH, H_2O, 22 °C; 96%. (k) 2 equiv $NaBH_4$, MeOH, 0 °C. (l) 10 equiv Li, NH_3, THF, −78 °C. (m) 1.2 equiv Dess−Martin periodinane, CH_2Cl_2, 0 °C; 73% overall from **13**. (n) 1.25 equiv LDA, 1.33 equiv TMSCl, THF; −78 °C; >95% regioselectivity, 95%. (o) O_3, 10 equiv $NaHCO_3$, CH_2Cl_2, MeOH, −78 °C; 10 equiv Me_2S; 83%. (p) 5 equiv LAH, Et_2O, 22 °C; 98%. (q) 1.2 equiv I_2, 1.2 equiv PPh_3, 1.8 equiv imid, C_6H_6, 22 °C; 86%. (r) 20 mol % CuI, 1.4 equiv $Me_2C{=}C(H)MgBr$, THF, 4 °C; 58%.

where the more classical cuprate reagents prove inadequate. The total synthesis also showcases the special activity of Ru complex **3** in promoting olefin cross-metathesis reactions.[8,9]



2
Ligand for additions to acyclic disubstituted enones



3
Catalyst for olefin metathesis

Results and Discussion

In the first section, the final synthetic route is presented (Scheme 1). In subsequent sections, more detailed studies that shed light on inner workings of several catalytic processes encountered in the total synthesis will be discussed.

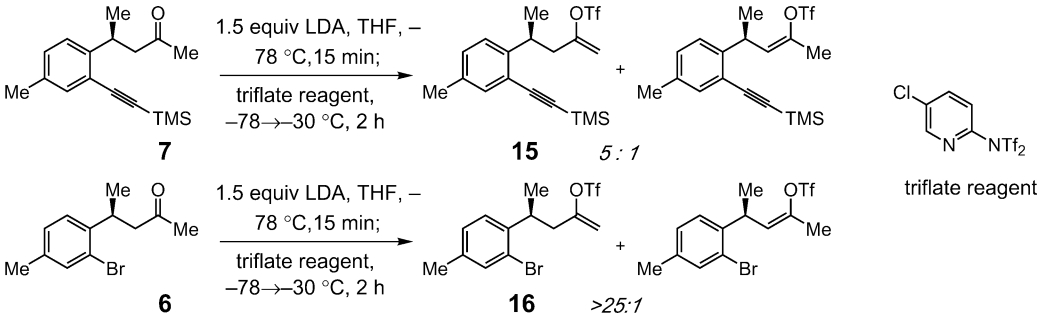
1. Enantioselective Total Synthesis of Erogorgiaene. Heck coupling of methyl vinyl ketone with commercially available dihalide **4** under the Jeffery conditions afforded α,β-unsaturated ketone **5** in 88% isolated yield;[10] when $(PPh_3)_2PdCl_2$ was used as the catalyst in the presence of an amine base, the derived saturated ketone was isolated as the major product. Subjection of enone **5**, on multigram scale, to 2.4 mol % chiral phosphine **2** and 1.0 mol % $(CuOTf)_2{\cdot}C_6H_6$ in the presence of 3 equiv of Me_2Zn (48 h, at −15 °C) delivered β-methyl ketone **6** in 94% isolated yield and >98% ee. At this point, a Pd-catalyzed Stille coupling with 5 mol % $Pd(PPh_3)_4$ and 1.2 equiv of $Bu_3SnCCSiMe_3$ at 100 °C afforded terminal alkyne **7** in 96% yield after silica gel chromatography. Attempts to obtain **7** through Pd-catalyzed Sonogashira coupling (10 mol % $(PPh_3)_2$-

(8) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(9) For an overview of chemistry regarding unique catalytic activity of Ru complex **3** and related derivatives, see: (a) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biol. Chem.*, in press. For representative examples, see: (b) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327−332. (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451−1454. (d) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−432. (e) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796−1797. (f) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606. (g) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038−4040. (h) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963−966. (i) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403−2405. (j) Royer, F.; Vilain, C.; Elkaim, L.; Grimaud, L. *Org. Lett.* **2003**, *5*, 2007−2009. (k) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691. (l) Lazarova, T.; Chen, J. S.; Hamann, B.; Kang, J. M.; Homuth-Trombino, D.; Han, F.; Hoffmann, E.; McClure, C.; Eckstein, J.; Or, Y. S. *J. Med. Chem.* **2003**, *46*, 674−676. (m) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927−2930. (n) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Bohm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941−944.

(10) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

Scheme 2 [a]



[a] Although one stereoisomer is shown, the stereochemical identity of the trisubstituted enol ethers has not been determined.

$PdCl_2$, 2 mol % CuI, $HCCSiMe_3$, Et_3N, DMF, 75 °C) led to sluggish transformations that gave rise to complex mixtures of products (<50% conv after 14 h).

As illustrated in Scheme 1, kinetic enolization through treatment of **7** with LiTMP and TMSCl (THF, −78 °C) led to the formation of the desired silylenol ether **8** with 9:1 regioselectivity and 97% overall yield. This selectivity, obtained through the use of sterically hindered LiTMP, came after extensive experimentation to identify conditions that would avoid the surprisingly low levels of enolization regioselectivity. As an example (Scheme 2), when LDA (1.5 equiv, THF, −78 °C, 0.5 h) was used as the base, only 5:1 selectivity (in favor of **15**) was observed. In contrast, when bromide **6** was treated with LDA at −78 °C, the desired kinetic enol ether **16** was obtained with >25:1 regiocontrol.[11] These observations suggest that preassociation of the lithium amide with the alkyne π system directs the deprotonation to occur at the more sterically hindered methylene site. This possibility finds support in a recent finding regarding alkyne-directed conjugate addition of alkyl cuprates to unsaturated esters[12] and several Pd-catalyzed cyclizations reported more than a decade ago.[13]

Conversion of enol ether **8** to alkene **9** (Scheme 1), the starting material for a metal-catalyzed enyne metathesis, was accomplished through a Pd-catalyzed reduction[14] of the derived enol triflate, which was generated upon sequential treatment of **8** with MeLi and Tf_2NPh.[15] It is noteworthy that when the enol triflate reduction was attempted in the presence of 5 mol % $PdCl_2$(dppf) and Et_3SiH,[16] the corresponding disubstituted olefin (product of olefin isomerization of **9**) was isolated as the exclusive product (1:1 mixture of alkene stereoisomers).

Treatment of enyne **9** with 5 mol % Ru catalyst **3**[8] (CH_2Cl_2, 22 °C) generated diene **10** in 84% yield after silica gel chromatography.[17] Subsequent treatment of **10** with 10 mol % **3** in the presence of 2 equiv of methyl vinyl ketone resulted in the formation of α,β-unsaturated ketone **11** in 74% isolated yield (>95:5 *E*:*Z*).[18] Attempts to effect conversion of **9** to **11** in a one-pot operation resulted in the formation of the desired product in <20% yield. In contrast, filtration of the unpurified **10** through a plug of silica gel before its subjection to a fresh batch of **3** and methyl vinyl ketone resulted in clean cross-metathesis. Attempts to effect conversion of **10** to **11** in the presence of Grubbs's second generation catalyst[19] led to formation of side products and lower reaction rates (70% recovered starting material vs 20% with **3** after 3 h).

Diastereoselective conjugate addition of Me_2Zn to enone **11** was carried out in the presence of 12 mol % chiral phosphine **12**, 5 mol % $(CuOTf)_2 \cdot C_6H_6$, and Me_2Zn (toluene, 4 °C); the desired ketone **13** was obtained in excellent diastereoselectivity (97:3), high regioselectivity (1,4:1,6 = 9:1), and 50% yield after silica gel chromatography (see below for more details on this transformation). It is noteworthy that when dipeptide ligand **2** was used in this reaction (vs **12**), although high enantioselectivity was obtained for the desired product (92% ee), the conjugate addition proceeded with significantly lower regioselectivity (1,4:1,6 = 1.5:1).

Diastereoselective reduction of the trisubstituted alkene in **13** was effected in three highly efficient steps, as catalytic or ionic hydrogenation of this substrate under a variety of conditions afforded the undesired isomer predominantly. Thus, treatment of **13** with $NaBH_4$ and subjection of the resulting secondary alcohol to dissolving metal conditions (Li/NH_3 at −78 °C) and reinstallation of the ketone group through a Dess−Martin oxidation afforded **14** in 73% overall yield and with 85:15 diastereoselectivity;[20] the desired diastereomer was obtained in the pure form after silica gel chromatography. Protection of the ketone group was required as the dissolving metal reduction in the presence of the carbonyl moiety led to the formation of significant amounts of undesired compounds.

The total synthesis was completed through conversion of the ketone in **14** to the derived primary alcohol in 77% overall yield (via the corresponding carboxylic acid). Conversion of the primary alcohol to the terminal iodide was followed by Cu-catalyzed alkylation in the presence of 1.4 equiv of 2-propenylmagnesium bromide[21] to provide optically pure erogor-

(11) Bromide **16** was not used in the total synthesis, since the terminal olefin derived from the Pd-catalyzed reduction (cf. **8** → **9**, Scheme 1) could not be induced to undergo efficient cross-coupling reactions. This may be due to interception of the organopalladium intermediates by the π cloud of the neighboring olefin.

(12) Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 1803−1806.

(13) Trost, B. M.; Tasker, A. S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670−672.

(14) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

(15) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.

(16) Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1348−1350.

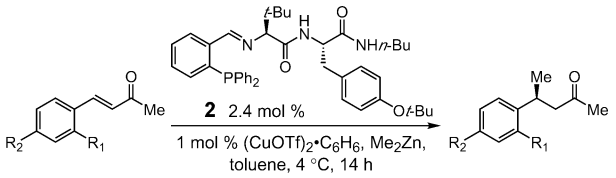
(17) For an earlier example where enyne ring-closing metathesis is used to synthesize dihydronaphthalenes, see: Rosillo, M.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Tetrahedron Lett.* **2001**, *42*, 7029−7031.

(18) For selected previous examples of sequential enyne ring-closing metathesis/cross-metathesis, see: (a) ref 9l. (b) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855−1858.

(19) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (b) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153−3155. (c) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417−10418.

(20) For alternative approaches to control of this 1,4-relative stereochemistry in a related class of compounds, see: (a) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1992**, 541−547. (b) LeBrazidec, J.-Y.; Kocienski, P. J.; Connolly, J. D.; Muir, K. W. *J. Chem. Soc., Perkin Trans 1* **1998**, 2475−2477.

Table 1. Cu-Catalyzed Asymmetric Conjugate Additions to Various 4-Phenyl-3-butene-2-ones



entry	R_1	R_2	conv (%)[a]	yield (%)[b]	ee (%)[c]
1	H	H	<10	nd[d]	86
2	H	CF_3	50	nd	91
3	H	OMe	<10	nd	nd
4	OMe	H	>95	44	94
5	OPh	H	>95	60	98
6	F	H	85	34	97
7	Me	H	19	nd	91

[a] Conversions determined by analysis of 400 MHz ^{1}H NMR spectrum of unpurified product mixtures. [b] Isolated yields of purified products after silica gel chromatography. Yields are unoptimized. [c] Determined by chiral GLC and HPLC analysis (see the Supporting Information for details). [d] nd = not determined.

giaene **1**. The synthetic material is identical to the natural compound based on comparison of ^{1}H NMR, ^{13}C NMR, LRMS, HRMS, and optical rotation.

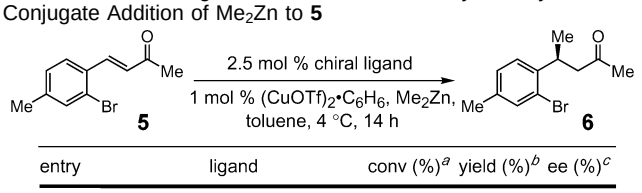
2. Studies Regarding Cu-Catalyzed Asymmetric Conjugate Addition of Me_2Zn to Enone 5. The efficient and enantioselective Cu-catalyzed ACA of Me_2Zn to unsaturated ketone **5** was an unexpected finding because, in general, β-aryl-substituted acyclic enones are not effective substrates for this class of reactions.[6a] For example, as illustrated in entry 1 of Table 1, when a similar substrate bearing an unsubstituted phenyl group is used, <10% conversion to the desired product is observed. To gain further insight regarding the positive influence of the *o*-Br substituent in **5** (i.e., steric vs electronic effects), we examined Cu-catalyzed additions of Me_2Zn to analogous substrates; the results of these studies are summarized in Table 1.

Comparison of the data in entries 2 and 3 of Table 1 suggests that electron-deficient aryl enones undergo Cu-catalyzed ACA more readily and the positive effect of the Br substituent in **5** may only be partially due to electronic factors. The results in entries 4−6 of Table 1 indicate that the presence of a substituent at the ortho site of the phenyl ring ($R_1 \neq H$), regardless of whether it is electron-donating (entries 4−5) or electron-withdrawing (entry 6), is beneficial to the rate of Cu-catalyzed ACA. Comparison of data in entries 4 and 5 suggests that oxygen-heteroatom chelation is likely not a key factor in determining reactivity. The lower rate of the reaction shown in entry 7 (R = Me) may be due to a prohibitive steric effect imposed by the larger Me substituent.[22] It is therefore plausible that the presence of an ortho group forces rotation of the aryl unit out of conjugation with the neighboring olefin, increasing the reactivity of the enone toward Cu-catalyzed addition. However, if the ortho substituent is too large, the steric bulk serves to inhibit addition.

Another noteworthy aspect of the Cu-catalyzed addition of Me_2Zn to enone **5** (see Scheme 1) is in connection to the identity

(21) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans 1* **2000**, 3578−3764.
(22) This argument is consistent with the A values reported for OMe, OPh, and Me groups (0.75, 0.65, and 1.74, respectively). See: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley-Interscience: New York, 1994; pp 696−697.

Table 2. Effect of Ligand Structure on Cu-Catalyzed Asymmetric Conjugate Addition of Me_2Zn to **5**



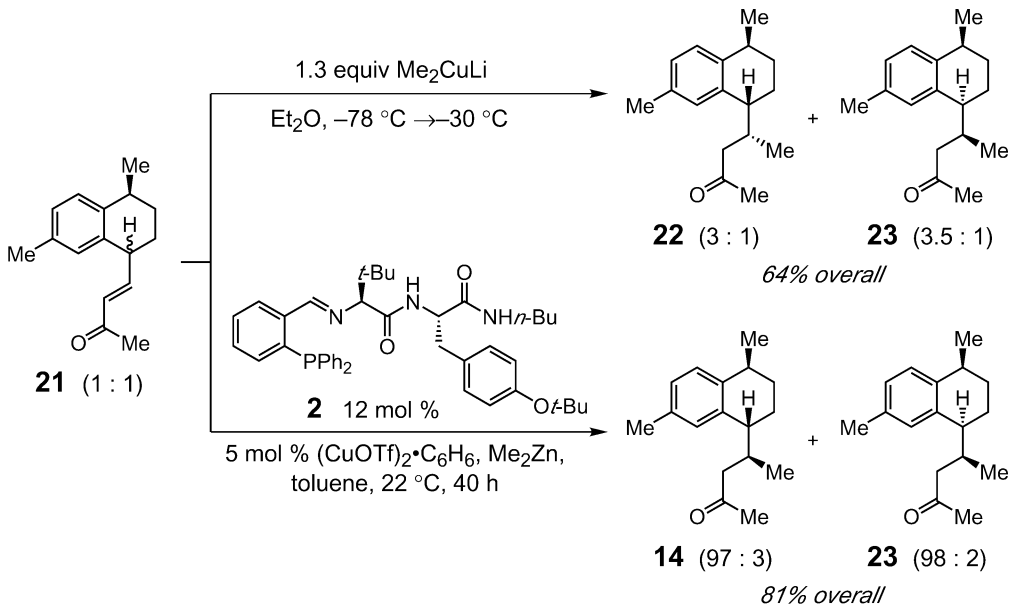
entry	ligand	conv (%)[a]	yield (%)[b]	ee (%)[c]
1	**2**	>95	91	95
2	**17**	30	nd	87
3	**18**	65	nd	<10
4	**19**	54	nd	89
5	**12**	>95	71	97
6	**20**	>95	73	98

[a] Conversions determined by analysis of 400 MHz ^{1}H NMR spectrum of unpurified product mixtures. [b] Isolated yields of purified products after silica gel chromatography. [c] Determined by chiral GLC analysis (see the Supporting Information for details). [d] nd = not determined.

of the optimal chiral ligand; key data obtained are depicted in Table 2. In contrast to Schiff base **2**, amine dipeptide **17** (entry 2, Table 2) is significantly less efficient in promoting C−C bond formation (30% conv and 87% ee vs >98% conv and 95% ee with **2**). The derived amide phosphine **18** (entry 3) is less effective than **2** and delivers nearly racemic products under the same conditions. As shown in entry 4 of Table 2 (ligand **19**), replacement of L-*t*-Leu at the AA1 site with L-Val leads to lower conversion and enantioselectivity as well.

It should be noted that, as illustrated in entries 5 and 6 of Table 2, chiral ligands bearing a *single* amino acid moiety, including Schiff base **20** bearing inexpensive L-Val, readily promote the enantioselective addition of Me_2Zn to enone **5**. However, in comparison to ACA catalyzed by dipeptide **2**, transformations effected by **12** and **20** provide unidentified byproducts and, as a result, lower isolated yields of the desired ketone (71−73% vs 91% yield with **2**). Comparison of data in entries 1, 4, 5, and 6 points to some degree of cooperativity between AA1 and AA2 segments of dipeptidic chiral ligands: whereas installment of L-Tyr(O*t*-Bu) as AA2 enhances the performance of a ligand that carries L-*t*-Leu as AA1 (entry 5 vs

Scheme 3. Control of Relative Stereochemistry through Cu-Catalyzed ACA Reactions[a]



entry 1), incorporation of L-Phe as AA2 is deleterious to the catalytic activity of a chiral ligand that has L-Val as AA1 (entry 6 vs entry 4).

3. Studies Regarding Stereoselective Cu-Catalyzed Conjugate Addition of Me_2Zn to Acyclic Enone Intermediates (cf. **11** → **13** in Scheme 1)**.** With a *chiral* substrate, generation of new stereogenic centers is often influenced by those that are already present in the molecule.[23] In this context, the use of chiral optically pure reagents or catalysts for control of stereochemistry ("reagent control") is an attractive strategy in synthesis, particularly when internal relay of stereochemistry ("substrate control") is unlikely due to the remoteness of a neighboring stereogenic center(s). There are also instances where asymmetric induction, even by a proximal stereogenic center, is ineffective. In such cases, a chiral catalyst can only be used if it is able to override completely the inherent preference for induction of stereochemistry imposed by the adjacent stereogenic site. That is, chiral ligand—and not the neighboring stereogenic center—must serve as the source of asymmetric induction.

The data presented in Scheme 3 were obtained while we investigated alternative approaches to establishing the stereochemistry of the side-chain Me group of erogorgiaene.[24] These findings indicate that in the Cu-catalyzed ACA to acyclic enones, the stereochemical identity of the product may not be affected by stereogenic sites present within the substrate but is largely dictated by the chiral ligand. Thus, treatment of a 1:1 mixture of diastereomers of **21**[25] with Me_2CuLi resulted in the formation of a 3−3.5:1 ratio of stereoisomers (each) of **22** and **23** (neither set bears proper stereochemistry for use in the total synthesis of erogorgiaene). In contrast, with Cu-catalyzed addition of Me_2Zn in the presence of chiral ligand **2**, *both* substrate diastereomers undergo highly stereoselective conjugate addition to afford **14** and **23** (96:4), regardless of the stereochemical identity of the adjacent site.

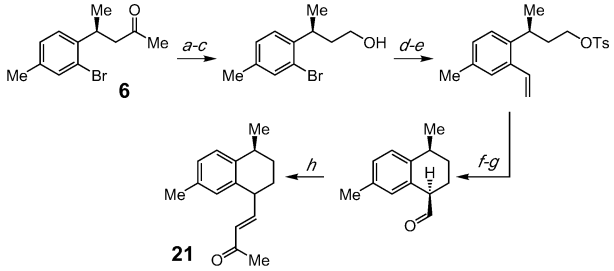
(23) For a review of substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(24) For a related example involving diastereoselective conjugate addition of a cuprate, see: Benoit-Marguie, F.; Csaky, A. G.; Esteban, G.; Martinez, E.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 3355−3358.

Conclusions

Through the enantioselective total synthesis of erogorgiaene we have illustrated the utility and demonstrated several critical aspects of Cu-catalyzed ACA of alkylzincs to acyclic α,β-unsaturated ketones. These studies demonstrate that in a synthesis scheme the catalytic process may be utilized to control absolute and relative stereochemistry. Together with catalytic metathesis reactions, both as a means to functionalize products of conjugate additions (e.g., Ru-catalyzed RCM of **9** to obtain **10** in Scheme 1) and as a way to access enones for additional C−C bond-forming transformations (e.g., Ru-catalyzed cross-metathesis of **10** to obtain **11**), catalytic ACA can be used to access a range of enantio- and diastereomerically pure cyclic and acyclic products. Another lesson learned from this study is that the versatility of amino acid-based ligands is not confined to screening of various dipeptidic systems; in certain cases, chiral ligands bearing a single amino acid should also be carefully examined (e.g., **11** → **13** in Scheme 1).[26]

(25) Compound **21** was prepared through Zr-catalyzed intramolecular olefin alkylation, as shown below. See: (a) Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395−398. For related studies, see: (b) de Armas, J.; Kolis, S. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 5977−5983. (c) de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097−2100. (d) Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9201−9204.



(a) 1.5 equiv LDA, 1.5 equiv TMSCl, THF, −78 °C. (b) O_3, 1.5 equiv pyr; 4 equiv Me_2S, 96% for two steps. (c) 1.3 equiv LAH, THF/Et_2O, −50 °C → 4 °C; 90%. (d) 10 mol % $PdCl_2(PPh_3)_2$, 700 psi ethylene, 3 equiv Et_3N, DMF, 90 °C, 93%. (e) 1.2 equiv TsCl, pyr, 0 °C → 22 °C, 93%. (f) 5 mol % Cp_2ZrCl_2, 5 equiv (2-cyclohexyl)ethylmagnesium bromide, THF, 55 °C; O_2, THF, 0 °C; 61% (7:1 diastereomeric ratio). (g) 1.2 equiv Dess−Martin periodinane, CH_2Cl_2, H_2O, 22 °C; 95%. (h) 1.1 equiv NaH, 1.2 equiv $(MeO)_2P(O)CH_2C(O)Me$, THF, 22 °C; 69% (1:1 diastereomeric ratio).

The present studies point to the need for additional ACA methods. For example, the synthesis sequence illustrated in Scheme 1 would be more concise if effective catalytic asymmetric conjugate additions of alkylmetals to unsaturated esters were to become available.[27] Studies toward the development of these and related catalytic enantioselective processes are in progress.

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Supporting Information Available: Experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For additional examples where related chiral ligands bearing a single amino acid have proven superior to the corresponding dipeptides, see: (a) ref 6e. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019.

(27) Attempted conjugate additions of Me_2Zn to unsaturated *N*-acyloxazolidinones (see ref 6b) corresponding to enones **5** (Scheme 1) and **21** (Scheme 3) proved to be highly inefficient. Such low rates of reaction are at least partially due to the fact that the typically less reactive Me_2Zn was employed.