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Efficient Construction of Polycyclic Derivatives via a Highly Selective Cu^{I}-Catalyzed Domino Reductive-Aldol Cyclization

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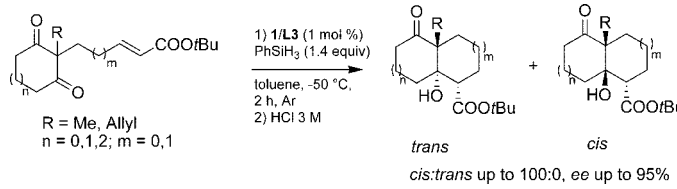
ABSTRACT



A versatile methodology for the diastereo- and enantioselective domino reductive-aldol cyclizations is reported. By using a copper (I)/diphosphane ligand, various five- and six-membered rings were generated with good to excellent diastereo- and enantioselectivities (cis:trans up to 100:0 and ee up to 95%).

The asymmetric construction of polycyclic compounds represents an important challenge in organic synthesis. These skeletons are often basic building blocks for the synthesis of biologically active natural products. Therefore, the use of tandem, domino, or cascade processes is a powerful tool to enhance the synthetic efficiency.[1,2]

Recently, excellent progress has been achieved in the area of reductive-aldol reactions for the construction of several contiguous stereocenters in one-pot.[3] However, only few methodologies described the synthesis of bi- and tricyclic compounds by using the reductive-aldol cyclization.

Our team has recently described an efficient method for the diastereo- and enantioselective domino reductive-aldol reaction between methyl acrylate and a ketone[4a] or an aldehyde,[5] catalyzed by a copper (I) precursor combined with an appropriate chiral diphosphane, in the presence of an organosilane as reducing agent. These promising results prompted us to investigate the scope of this methodology for the synthesis of polycyclic compounds.

These reactions are proposed to proceed by the in situ formation of a metal enolate through the conjugated addition of a metal hydride specie onto the Michael acceptor. Then, the intramolecular nucleophilic attack on the electrophile formed the aldol-type adduct after a final reaction with the hydride source. The domino reductive-aldol reactions take the advantage of avoiding the preactivation of the nucleophile (metal-enolate) in an independent step in contrast to the Mukaiyama-type reactions.[6]

Our initial experiment was conducted with a catalytic amount of the air stable precatalyst $CuF(PPh_3)_3$•2MeOH[7] **1** and (*S*)-MeO-BIPHEP **L1** (1 mol %) on the diketo-ester **2a** (R = Et),[8] in the presence of phenylsilane as the hydride source at room temperature.

We were pleased to observe a complete conversion onto the single product **3a** after 2 h of reaction. Moreover, only

(1) Reviews on domino reaction: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.

(2) For reviews on domino, cascade reactions in total synthesis see: (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Comm.* 2003, 551−564. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (d) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.

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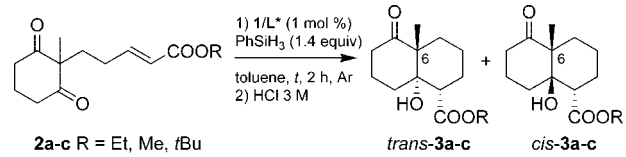
two diasteroisomers[9] *cis*-**3a** and *trans*-**3a** were formed over the four possible isomers and were isolated with a good 80% yield.[10] A trans selectivity was observed (*trans*-**3a**:*cis*-**3a** 68:32), albeit with a low enantioselectivity (ee(*trans*-**3a**):23%) for the major *trans*-**3a** isomer. We then studied the influence of different parameters. The most representative results are summarized in Table 1.

When the (*S*)-MeO-BIPHEP ligand **L1** was used at −50 °C, we observed a significant improvement of the enantioselection of the *trans* isomer with a slight increase of the *cis:trans* ratio (Table 1, entries 2 versus 1). We then screened a wide range of chiral diphosphane ligands and found that the TaniaPhos ligands **L2**−**L5** gave the best selectivities, without any loss of the excellent reactivity of the catalytic system (Figure 1).[11] Although a low *cis:trans* selectivity was observed at room temperature, a promising ee of 82% was reached for the cis isomer with the TaniaPhos ligand **L2** (Table 1, entry 3). A slight enhancement of the cis:trans ratio and the enantioselectivity was again observed when the reaction was carried out at −50 °C (Table 1, entry 4), and this temperature was then kept for further optimizations.

Increasing the steric bulkiness around the phosphorus atom with the ligand **L3** gave further improvement of both *cis:trans* ratio to 82:18 and an excellent enantioselectivity of 92% for the major *cis*-**3a** isomer (Table 1, entry 5). We also noticed a similar enantioselectivity with the hydroxy analogue TaniaPhos **L4** (Table 1, entry 6 versus 5).

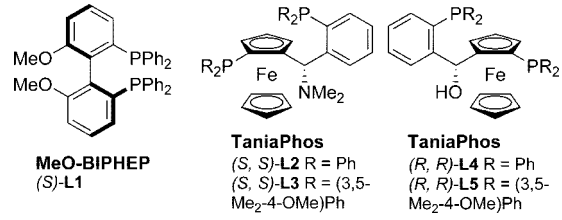
Table 1. Asymmetric Copper-Catalyzed Reductive-Aldol Cyclization of Substrate **2a**−**c** Catalyzed by $CuF(PPh_3)_3$•2MeOH **1**/**L***[a]



2a-c R = Et, Me, *t*Bu — *trans*-**3a-c** — *cis*-**3a-c**

entry	**2**	**L***	temp (°C)	*cis*-**3**:*trans*-**3**[b]	ee(*cis*-**3**)/ee(*trans*-**3**) (%)[b]
1	**2a**	**L1**	25	32:68	14/23
2	**2a**	**L1**	−50	24:76	35/70
3	**2a**	**L2**	25	57:43	82/47
4	**2a**	**L2**	−50	68:32	89/63
5	**2a**	**L3**	−50	82:18	92/33
6	**2a**	**L4**	−50	73:27	−91/−72
7	**2b**	**L3**	−50	72:28	84/60
8	**2c**	**L2**	−50	100:0	86
9	**2c**	**L3**	−50	100:0	95
10	**2c**	**L4**	−50	100:0	−86
11	**2c**	**L5**	−50	100:0	−95

[a] Reactions were carried out in a 0.1 M solution in toluene at the indicated temperature under an oxygen free argon-atmosphere in presence of **2a**−**c** (1 mmol), $CuF(PPh_3)_3$•2MeOH **1** (1 mol %), chiral ligand L* (1 mol %) and phenylsilane (1.4 equiv) for 2 h. [b] *cis:trans* ratio and enantiomeric excesses were determined by chiral GC analysis; see Supporting Information for details.



MeO-BIPHEP (*S*)-**L1**

TaniaPhos (*S, S*)-**L2** R = Ph; (*S, S*)-**L3** R = (3,5-Me_2-4-OMe)Ph

TaniaPhos (*R, R*)-**L4** R = Ph; (*R, R*)-**L5** R = (3,5-Me_2-4-OMe)Ph

Figure 1. MeO-BIPHEP Ligand and TaniaPhos-type Ligands.

(3) For reviews on reductive-aldol reactions see: (a) Chiu, P. *Synthesis* 2004, 2210−2215. (b) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137. Selected references: for intermolecular reductive-aldol reaction [Rh]: (c) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202–12203. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529. (e) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972–6973. (f) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156–15157. (g) Jung, C. K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051–17056. (h) Bee, C.; Han, S. B.; Hassan, A.; Lida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747[Ir]: (i) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829–1831[Co]: (j) Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367–4370. For intramolecular reductive-aldol reaction [Rh]: (k) Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958. (l) Jang, H. Y.; rische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653–661. (m) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421–5424[Co]: (n) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113. (o) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448–9453. (p) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729–3732[Cu]: (q) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229–9232. (r) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Org. Lett.* **2001**, *3*, 1901–1903. (s) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091–4093. (t) Chiu, P.; Leung, S. K. *Chem. Comm.* **2004**, 2308–2309. (u) Chung, W. K.; Chiu, P. *Synlett* **2005**, 55–58. (v) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529. (w) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228. (x) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743–5746. When the preparation of this manuscript Lipshutz reported an enantioselective reductive-aldol reaction for the construction of cyclic compound: (y) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378–14379, All references about reductive aldol reaction are summarized in the Supporting Information.

(4) (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292–1297. In the same time, Shibasaki reported a similar catalytic system with low to moderate selectivities: (b) Zhao, D. B.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403–1407. For studies on the influence of the TaniaPhos structure see: (c) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441. For catalytic asymmetric reductive-aldol of allenic esters to ketones see: (d) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164–7165.

(5) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O. *Org. Lett.* **2006**, *8*, 5943–5946.

(6) (a) Mukaïyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (b) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645.

(7) $CuF(PPh_3)_3$•2MeOH was prepared according to a literature procedure: Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153–159.

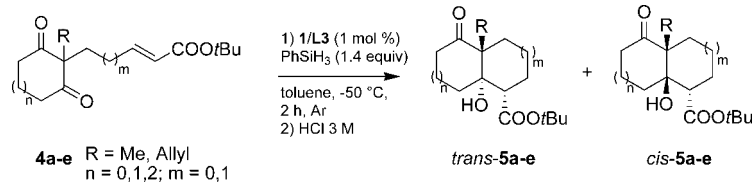
(8) The diketo-ester **2a** is easily prepared in two-steps, starting from the commercially available 2-methyl-1,3-cyclohexanedione. (a) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143–1146. (b) Thiemann, T.; Umeno, K.; Wang, J.; Tabuchi, Y.; Arima, K.; Watanabe, M.; Tanaka, Y.; Gorohmaru, H.; Mataka, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2090–2110.

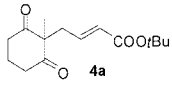
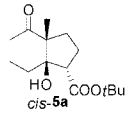
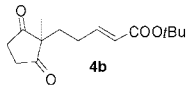
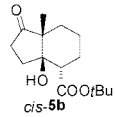
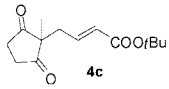
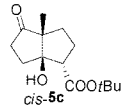
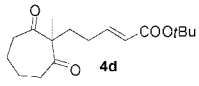
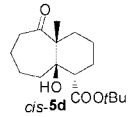
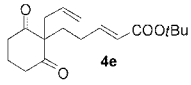
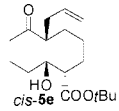
(9) Cis and trans nomenclature referred to the relation of the different substituents on the bicyclic junction.

(10) The relative configuration were determined by NOE experiments on each pure isolated isomers, see Supporting Information for details. The absolute configuration are determined on the dehydrated compound **6b** by comparison of the optical rotation value of the latter with the reported value $[\alpha]^{20}$ −85.6 (c = 3.4 in $CHCl_3$) and −140 (c = 2.1 in $CHCl_3$) the configuration is *S*. Yamazaki, J.; Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Watanabe, J.; Fuji, K. *Tetrahedron Asymmetry* **2002**, *13*, 729–734.

(11) Ferrocenyl ligands like JosiPhos, WalPhos and MandyPhos were also tested but gave low selectivities.

Table 2. Asymmetric Copper-Catalyzed Reductive-Aldol Cyclization of Substrate **2c** or **4a**−**e** Catalyzed by **1**/**L3***[a]



entry	4	5 [b]	yield (%) [c]	*cis*-**5**:*trans*-**5** [b]	ee(*cis*-**5**)/ee(*trans*-**5**) (%) [b]
1			85	94:6	80/85
2			80	89:11	97/72
3			85	100:0	66
4			85	100:0	94
5			70	100:0	94

[a] Reactions were carried out in a 0.1 M solution in toluene at indicated temperature under an oxygen free argon-atmosphere in presence of **4a**−**e** (1 mmol), $CuF(PPh_3)_3$•2MeOH **1** (1 mol %), chiral ligand L* (1 mol %) and phenylsilane (1.4 equiv) for 1 h. [b] *cis:trans* ratio and enantiomeric excesses were determined by chiral GC analysis. For details see Supporting Information. [c] Isolated yields of *cis*-**5a**−**e**.

We then studied the influence of the steric hindrance on the ester moiety of our precursors **2a-c**; if the bulkiness around the chiral copper enolate intermediate was increased, it might influence the course of the stereoselection of our model reaction. The domino process was first carried out on the substrate **2b** (R = Me) with the TaniaPhos ligand **L3** (table 1, entry 7); we noted that the selectivities were decreased as expected. The Substrate **2c** (R = *t*-Bu) was then tested with TaniaPhos ligands **L2**−**L4** (Table 1, entries 8−10), and in our delight, we found that the only *cis*-**3c** diastereoisomer was formed in all cases. When the bulkier ligands **L2** and **L5** were used, a 95% enantiomeric excess was finally obtained in both cases for the *cis* isomer *cis*-**3c**. This reaction proved to be highly reproducible and larger scale reactions could also be performed with an equal efficiency at lower catalyst loading. A 10mmol scale reaction was carried out with a 0.5 mol % loading of the copper/**L3** catalyst. A complete conversion was observed after 15 min at −50 °C and the bicyclic adduct *cis*-**3c** was isolated in a 80% yield and a 95% enantioselectivity.

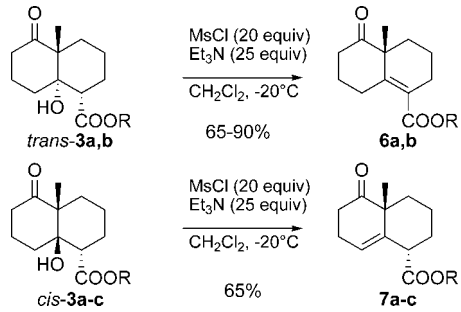
We then investigated the scope of this methodology on the synthesis of enantiomerically enriched bicyclic adducts bearing various ring sizes and substitutions under the previous optimized conditions (Table 2). All the cyclization precursors **2c** and **4a-e** were easily prepared by literature procedures (see Supporting Information). As mentioned earlier, only one *cis* diastereoisomer **3c** was formed from the C_2-symmetrical precursor **2c** with a 95% enantioselectivity. We observed the formation of 5-membered rings from precursors **5a** and **5c** (Table 2, entries 1 and 3), with excellent diastereoselectivity, albeit with moderate enantioselectivities. Indeed, a decrease in the enantioselection to 66% was measured for the 5,5-bicyclic adduct *cis*-**5c** while the 6,5-bicyclic adduct *cis*-**5a** was obtained with a reasonable 80% ee. However, the formation of 6-membered ring was carried out with excellent *cis*-selectivities as well as high enantioselectivities (Table 2, entries 2 and 4). However, under the optimized conditions, the substrates bearing longer lateral tether that could generate 7- an 8-membered rings, only result in simple reduction. Furthermore, by replacing the ester by a nitrile group, we observed the formation of only one *cis*-isomer but alas, with no enantiomeric excess.

We also checked the possibility to introduce different substituants on the quaternary carbon of the precursors **4e** (Table 2, entry 5); the reductive-aldol cyclization was achieved on the allyl precursor **4e** and the resulting allyl-substituted bicyclic adduct *cis*-**5e** was isolated in a 70% yield as a single *cis*-isomer and a 94% enantiomeric excess. This substrate *cis*-**5e** behaved with equal efficiency compared to the methyl analogue *cis*-**3c**.

We found that an optimum procedure was built up with a preformed catalyst prepared in situ by a ligand exchange between the air stable precatalyst $CuF(PPh_3)_3$•2MeOH and the appropriate chiral ligand. As we have already noticed,[4a,5] this class of copper hydride species have shown a high reactivity toward the reductive-aldol cyclization. These results show that the combination of a straightforward access to the precursors, the low catalyst loading, a scalable procedure, and the high selectivities reached in most cases, should allow to an easy access to new chiral building blocks for asymmetric synthesis.

We next investigated access of synthetically useful scaffolds by studying the behavior of the 6,6-bicyclic adducts **3a**−**c** toward dehydratation (scheme 1). Indeed, the products

Scheme 1. Dehydratations of Bicyclic Adducts **3a**−**c**

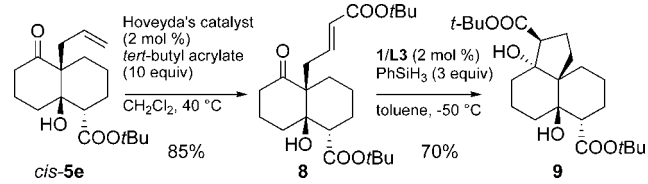


6a−**b** are often used in total synthesis and are prepared in several steps starting from the well-known Wieland-Miescher ketone.[12] By our method, only 4 steps are required to afford the enantio-enriched compound **6a**−**b**.

After several trials on the reagents and reaction conditions, it was found that mesyl chloride and triethylamine reacted smoothly with the bicyclic adducts *trans*-**3a** and *trans*-**3b** to give the conjugated unsaturated esters **6a,b** in good isolated yields. When those conditions were applied to the bicyclic adducts *cis*-**3a** and *cis*-**3c**, the dehydration occurred too, but the non conjugated alkenes **7a**, **7b**, and **7c** were the sole products in those reaction, and were isolated with 65% yields after purification.[13]

The possibility to use substitutions on the quaternary carbon of the cyclization precursors enabled us to consider the construction of new angular tricyclic compounds such as **9** by using the allyl-substituted bicyclic adduct *cis*-**5e** (Scheme 2).

Scheme 2. Formation of the Tricyclic Adduct **9**



The cross metathesis of the allyl group and *tert*butyl acrylate of adduct *cis*-**5e** was first carried out with a catalytic amount of the second generation Hoveyda's catalyst, and afforded the cyclization precursor **8** in a good 85% yield.[14] Then, the reductive-aldol cyclization of **8** was performed in our standard conditions, and we were finally pleased to observe the formation of the new expected angular tricyclic adduct **9** as a single diastereoisomer in a good 70% yield after purification.[15]

In summary, we have developed an efficient methodology for the construction of bicyclic scaffolds. The domino reductive-aldol cyclization, catalyzed by a copper (I) precursor combined with the appropriate chiral diphosphane ligand in the presence of phenylsilane, is highly diastereo- and enantioselective for a range of different substrates and enabled us to prepare various bicylic compounds in an enantiomerically enriched form. Moreover, this strategy has also been successfully extended to the synthesis of a new angular tricyclic compound. This versatile method may be used to synthesize more highly substituted molecules. Current efforts are focused on using these building blocks for the synthesis of biologically active compounds. Further studies in this area will be reported in due course.

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Supporting Information Available: Experimental details, spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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