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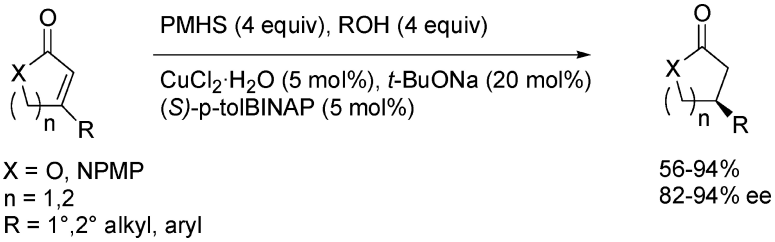
J. Am. Chem. Soc., **2003**, 125 (37), 11253-11258• DOI: 10.1021/ja0351692 • Publication Date (Web): 19 August 2003



X = O, NPMP
n = 1,2
R = 1°,2° alkyl, aryl

56-94%
82-94% ee

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Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams

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Abstract: A dramatic acceleration of the enantioselective copper-catalyzed conjugate reduction of α,β-unsaturated lactones, lactams, and esters is reported upon addition of alcohol additives. Good to excellent yields and enantioselectivities were realized using a catalyst generated in situ from $CuCl_2 \cdot H_2O$, *t*-BuONa, *p*-tol-BINAP, and PMHS, and this methodology was applied to the synthesis of (−)-Paroxetine.

Introduction:

Chiral lactones and lactams possessing a β-stereocenter are found within a number of biologically active compounds such as the lignans (−)-Trachelogenin (**1**) and (−)-Arctigenin (**2**), and antidepressant/PDE IV inhibitor (−)-Rolipram (**3**).[1] Five- and six-membered lactams also serve as precursors to pyrrolidines and piperidines, which are found within a number of important pharmaceuticals such as the antidepressant (−)-Paroxetine (**4**) (Figure 1).[2]

Despite recent developments in metal-catalyzed conjugate addition methodology,[3] there are few reports whereby these compounds can be accessed in either racemic or enantiomerically enriched form by 1,4-addition of organometallic nucleophiles to unsaturated precursors. Conjugate addition to butenolides typically requires the incorporation of an additional activating substituent, such as a sulfide or a selenide, at the α-position.[4] In the only example of a catalytic enantioselective addition to unsaturated five-membered ring lactones that we are aware of, Hayashi has shown that a Rh(I)/(BINAP) complex catalyzes the addition of phenyl boronic acid to butenolide in 33% yield and 97% ee.[5] This methodology was also successful for the addition of aryl boronic acids to pentenolide[5] and to unsaturated six-membered lactams.[6] There also have been reports describing the enantioselective additions of *n*-alkyl Grignard reagents or diethyl zinc to pentenolide using catalytic amounts of chiral copper complexes.[7]

We have recently described the use of a Cu(I)/*p*-tolBINAP catalyst for the enantioselective 1,4-reduction of acyclic α,β-unsaturated esters and cyclic enones using PMHS (polymethylhydrosiloxane) as a stoichiometric reductant.[8] We report herein our efforts to extend this methodology to the conjugate reduction of lactones and lactams. During the course of these studies, mechanistic considerations led to the discovery that alcohol additives improve the yields and dramatically increase the rates of reduction of these substrates.[9] This improved protocol has allowed for an efficient synthesis of (−)-Paroxetine.

Results

The starting materials for this investigation were prepared as shown in Scheme 1. Our initial approach to β-substituted butenolides involved ring-closing metathesis (RCM) of dienes **5a**−**c**,[10] prepared by esterification of allylic alcohols which were either purchased from commercial sources or prepared by copper-catalyzed addition of Grignard reagents to propargyl alcohol.[11] When these acrylates were treated with 5 mol % of ruthenium carbene **7** for 18 h in refluxing dichloromethane, 65% conversion to the desired product was observed. Interestingly, increasing the catalyst loadings to 7 mol % led to only 35%

(1) For lead references regarding natural products containing chiral lactones, see: (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, pp 476−541. (b) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675 and references therein. (c) For synthetic approaches to Rolipram, see: Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775 and references therein.

(2) For synthetic approaches to (−)-Paroxetine, see: (a) Christensen, J. A.; Squires, R. F. German Patent 2,404,113, 1974. U.S. Patent 3,912,743, 1975. U.S. Patent 4,007,196, 1977; *Chem Abstr.* **1974**, *81*, 152011q. (b) Faruk, E. A.; Martin, R. T. EP Patent 223,334, 1986; *Chem. Abstr.* **1987**, *107*, 96594y. (c) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*. 5647. (d) de Gonzalo, G.; Brieva, R.; Sánchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem.* **2001**, *66*, 8947 and references therein. For a formal synthesis of (−)-Paroxetine, see ref 6.

(3) For recent reviews of asymmetric conjugate addition, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(4) (a) Bella, M.; Piancatelli, G.; Pigro, M. C. *Tetrahedron* **1999**, *55*, 12387. (b) Hollingworth, G. J.; Lee, T. V.; Sweeney, J. B. *Synth. Commun.* **1996**, *26*, 1117. (c) Watanabe, M.; Tsukazaki, M.; Hirakawa, Y.; Iwao, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989,** *37*, 2914.

(5) (a) Tayaka, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron:Assymetry* **1999**, *10*, 4047. For catalytic enantioselective approaches to γ-lactones and γ-lactams having a β-stereocenter featuring Rh(II)-catalyzed intramolecular C−H insertions, see: (b) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146. (c) Anada, M.; Hashimoto, S. *Tetrahedron Lett*. **1998**, *39*, 79. See also ref 1d.

(6) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.

(7) (a) Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett*. **2002**, *43*, 1189. (b) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843. (c) Yan, M.; Zhou, Z.-Y.; Chan, A. *J. Chem. Soc., Chem. Commun.* **2000**, 115.

(8) (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (c) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. Important related work: Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580.

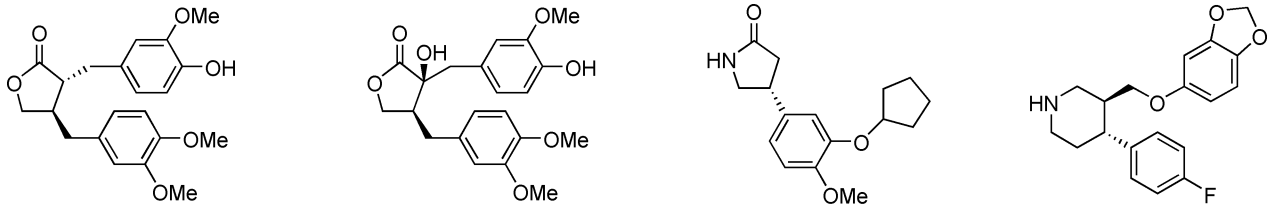
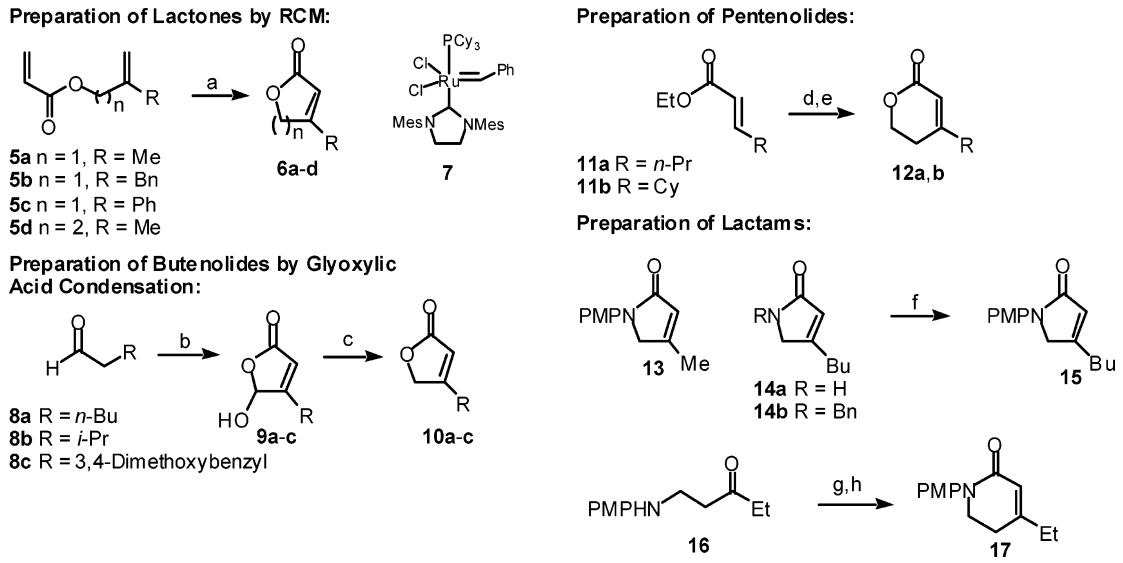


Figure 1. Biologically active compounds containing chiral lactones and lactams.

Scheme 1. Preparation of Unsaturated Lactones and Lactams[a]



[a] (a) **7** (1−1.5 mol %), 10 h syringe pump addition, CH_2Cl_2, reflux, 40−90%. (b) $HCOCO_2H{\cdot}H_2O$ (1 equiv), piperidine hydrochloride (1.1 equiv), dioxane/H_2O, reflux, 18 h. (c) $NaBH_4$ (1 equiv), MeOH, 60−79% (two steps). (d) $Ru(CO)(H)_2(Ph_3P)_3$ (5−20 mol %), $CH_2{=}CHSi(OEt)_3$ (2 equiv), toluene, reflux, 0.5−3 h. (e) H_2O_2, NaF, $NaHCO_3$, THF, 30−60%. (f) *p*-iodoanisole (1.1 equiv), K_3PO_4 (1.3 equiv), CuI (5 mol %), $MeNH(CH_2)_2NHMe$ (20 mol %), toluene 80 °C, 91%. (g) $ClCOCH_2CO_2Et$, Na_2CO_3, H_2O/CH_2Cl_2. (h) EtONa (4 equiv), EtOH, reflux, 18 h, 70% (two steps).

conversion under otherwise identical conditions. When 2 mol % of **7** was added in a single portion to a solution of **5** in refluxing dichloromethane, 95% conversion was achieved after 2 h. Adding 1 mol % of **7** as a solution in dichloromethane over 10 h resulted in complete conversion of **5a** and **5b**, with slightly higher loadings (1.5 mol %) being required for complete conversion of **5c**.[12] Pentenolide **6d** was also prepared using this protocol.

It was possible in some cases to use a condensation/reduction strategy as an operationally simple and inexpensive alternative to the RCM methodology. Hydroxy butenolides **9a**−**c**, which were prepared by condensation of aldehydes **8a**−**c** and glyoxylic acid in the presence of piperidine hydrochloride, could be treated with sodium borohydride to afford the desired lactones **10a**−**c**.[13]

Pentenolides **12a** and **12b** were prepared from β-substituted acrylates **11a** and **11b** using a minor variation of a literature procedure involving Ru-catalyzed coupling with a vinyl silane, followed by oxidation of the C−Si bond with concomitant lactonization.[14]

Five-membered lactams **13** and **14a** were prepared according to literature procedures.[15] Conversion of **14a** to **15** was affected by our recently developed Cu-catalyzed amide arylation methodology.[16] Six-membered lactam **17** was prepared from **16** by amidation with ethylmalonyl chloride, followed by intramolecular Knovenagel condensation and a retro-Claisen decarboxylation.

(9) After this manuscript was submitted, we became aware of prior work of Stryker. Specifically, he has reported three examples with three substrates in which the use of *t*-BuOH as an additive (10−15 equiv) allowed for the catalytic conjugate reduction to be carried out at 1 atm of hydrogen using 10−17 mol % Cu in 24−48 h. In the best case, the reduction of carvone is reduced to a 87:13 ratio of the conjugate reduction product and the overreduced saturated alcohol.[1] The authors attribute the effect of the added *t*-BuOH to "a protolytic transfer process to quench the unstable intermediates with concomitant transfer of the copper to a more stable alkoxide moiety where hydrogen activation can proceed under lower pressure." Stryker has also demonstrated that the addition of *t*-BuOH often favors 1,2-reduction. (a) Lipshutz, B. H. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; p 167. (b) Stryker, J. M.; Mahoney, W. S.; Daeuble, J. F.; Brestensky, D. M. In *Catalysis in Organic Synthesis*; Pascoe, W. E., Ed.; Marcel Dekker: New York, 1992; p 29. (c) Daeuble, J. F.; Stryker, J. M. In *Catalysis of Organic Reactions*; Scaros, M., Prunier, M. L., Eds.; Marcel Dekker: New York, 1995; p 235. (d) Chen, J. X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (e) Chen, J. X.; Daeuble, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.

(10) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(11) Buboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

(12) This behavior is suggestive of a catalyst decomposition pathway that is second order in Ru. For a discussion of the mechanism of Ru carbene decomposition pathways, see: Choi, T.-L.; Lee, C. W.; Chatterjee, A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.

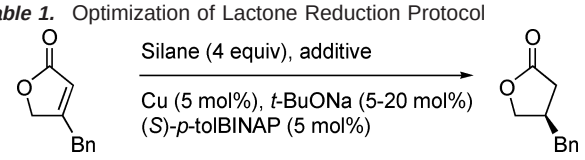
(13) (a) Bourguignon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889. (b) Bourguignon, J. J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C. G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893.

(14) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371.

(15) (a) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 4859. (b) Corriu, R. J. P.; Bolin, G.; Iqbal, J.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron* **1993**, *49*, 4603.

(16) (a) Klapers, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

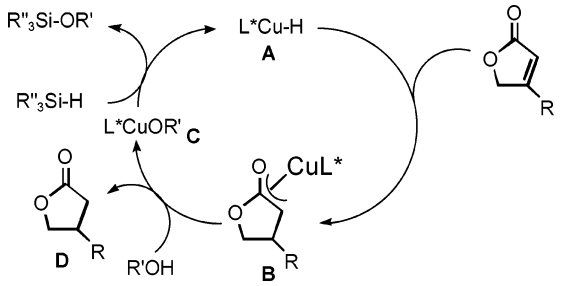
Table 1. Optimization of Lactone Reduction Protocol



entry	Cu/silane	solvent (ROH)	temp (°C) (time (h))[a]	% yield (% ee)[b]
1	CuCl/PMHS	$PhCH_3$	23 (48)	50 (80)
2	CuCl/Ph_2SiH_2	Et_2O/pent[c]	−15 (24)	34[d] (91)
3	CuCl/PMHS	*c*-hex (EtOH)[e]	23 (5 min)	89[f] (−)
4	CuCl/PMHS	THF/pent (EtOH)[c,e,g]	−40 (4)	90 (93)
5	$CuCl_2$·$2H_2O$/PMHS	$PhCH_3$/pent (*i*-PrOH)[e,h]	−20 (3)	90 (92)

[a] >95% conversion. [b] Isolated yields. % ee determined by HPLC. [c] 80% pentane. [d] 75% conversion. [e] 4 equiv of ROH. [f] GC yield, 10% residual starting material. [g] EtOH added by syringe pump over 4 h. [h] 20 mol % *t*-BuONa was used. 50/50 $PhCH_3$/pentane.

Scheme 2. Proposed Mechanism for the Copper-Catalyzed Lactone Reduction



When **6b** was subjected to the reaction conditions described in our initial report (Table 1, entry 1),[8a] the desired product was isolated in 50% yield and 80% ee, along with 5% residual starting material after 48 h (Table 1, entry 1). Using Ph_2SiH_2 in place of PMHS and switching to a predominantly hydrocarbon solvent system accelerated the reaction such that it could be performed at −15 °C (entry 2). While the enantiomeric excess improved to 91%, the isolated yield was still low (34% at 75% conversion).

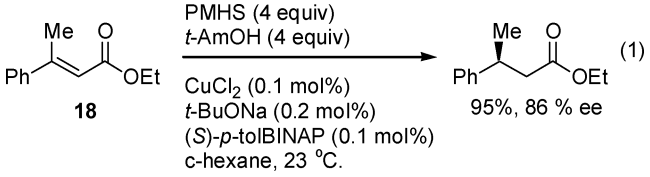
We have previously suggested that these conjugate reductions proceed via a copper enolate that undergoes σ-bond metathesis with a Si−H bond to form a silylketene acetal.[8a] If the poor mass balance was due to side reactions of either the copper enolate or the silylketene acetal, we postulated that better yields might be realized upon addition of an alcohol to protonate the enolate.[17] This would generate the lactone product (**D**, Scheme 2) and a copper alkoxide (**C**). We reasoned that **C** should be capable of undergoing σ-bond metathesis more rapidly than **B** to regenerate catalytically active **A** (vide infra).

We were pleased to find that adding EtOH (4 equiv) to a room temperature mixture of substrate, catalyst, and PMHS gave an 89% GC yield of the desired product at 90% conversion after 5 min (Table 1, entry 3). The reaction did not proceed beyond 90% conversion, presumably due to competitive silylation of EtOH with concomitant release of H_2.[18] Lowering the reaction temperature to −40 °C and adding EtOH via syringe pump over 4 h allowed for complete consumption of lactone, with the product being isolated in 90% yield and 93% ee (Table 1, entry 4). Switching from EtOH to *i*-PrOH obviated the need for slow addition. We also found that air-stable $CuCl_2$·$2H_2O$ could replace CuCl as the copper source, allowing the reaction to be set up without the aid of a drybox (Table 1, entry 5).

These conditions allowed for the reduction of *n*-alkyl (Table 2, entry 1), secondary (Table 2, entry 2), and benzyl (Table 2, entries 4,5) substituted butenolides in good yields with good to excellent levels of enantioselectivity. The reduction of **10c** represents a formal synthesis of lignans **1**[19] and **2**.[5b] Phenyl substituted butyrolactone was formed with only modest enantiomeric excess (entry 3).[20]

Initial attempts to extend this methodology to the reduction of pentenolides were again hampered by poor mass balance. For instance, the reduction of **12a** at −20 °C with 4 equiv of *i*-PrOH resulted in a GC yield of only 25% at 100% conversion. Switching to a larger alcohol additive, *tert*-amyl alcohol (*t*-AmOH), and lowering the reaction temperature to −40 °C significantly improved the GC yields (80−90%), although the isolated yields for these substrates are moderate (55−70%, Table 2, entries 6−8), and separation of the reduced products from byproducts required two chromatographic columns. As was the case for the reduction of cyclohexenones, BIPHEMP was found to be the ligand of choice for the reduction of pentenolides. We next examined the asymmetric conjugate reduction of lactams. While N−H and *N*-benzyl lactams **14a** and **14b** did not undergo reduction, *N*-*p*-methoxyphenyl lactam **15** was reduced in 94% yield and 94% ee after 3 h at 0 °C (Table 2, entry 9). The reduction of 4-methyl lactam **13**, which was considerably slower than that of **15**, was accelerated by switching solvents from 50/50 *c*-hexane/toluene to *c*-hexane/THF, presumably due to its insolubility in the former solvent system (entry 10). In contrast to cyclohexenones and pentenolides, reduction of unsaturated six-membered lactam **17** proceeds with excellent ee using *p*-tolBINAP as the ligand (entry 11).

The reduction of acyclic unsaturated esters was also accelerated by the addition of alcohols. Treatment of ethyl *trans*-β-methylcinnamate (**18**) with PMHS (4 equiv) and *t*-AmOH (4 equiv) with as little as 0.1 mol % Cu/(*S*)-*p*-tolBINAP allowed for complete consumption of **18** in 36 h (eq 1). By contrast, reduction of **18** with catalyst loadings of 1 mol % in the absence of alcohol additives required 48 h to achieve 95% conversion.



A series of alcohols of various sizes (EtOH, *i*-PrOH, 3-pentanol, *t*-AmOH) were screened to identify the optimal additive (Figure 1). The alcohols (4 equiv) were added via syringe pump over an hour to a mixture of **18** (1 equiv), $CuCl_2$ (0.5 mol %), *t*-BuONa (1 mol %), (*S*)-*p*-tolBINAP (0.5 mol

(17) For other examples of alcohols and amines accelerating metal-catalyzed silane reductions, see: (a) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103. (b) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640. (c) Hays, D. S.; Fu, G. C. *Tetrahedron* **1999**, *55*, 8815.

(18) In support of this, vigorous gas evolution, presumably H_2, was observed upon addition of EtOH.

(19) Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 6922.

(20) It should be noted that the reduction of β-methyl substituted butenolide continues to suffer from poor mass balance, even under optimized conditions.

Table 2. Enantioselective Conjugate Reduction of Lactones and Lactams[a]

Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1	**10a** R = n-Bu		89	86
2	**10b** R = i-Pr		87	92
3	**6c** R = Ph		70	71
4	**6b** R = H		90	92
5[d]	**10c** R = OMe		85	92
6[f]	**6d** R = Me		70	82
7[f]	**12a** R = n-Pr		71	86
8[f]	**12b** R = Cy		56	94
9[g,h]	**13** R = Me		90	92
10[g]	**15** R = n-Bu		94	94
11[g]	**17**		89	91

[a] Conditions from Table 1, entry 5. [b] Isolated yields, >95% pure. [c] % ee determined by GC or HPLC. [d] 20% CH_2Cl_2 was used to facilitate solvation. [e] 6 h was required for 100% conversion. [f] Recrystallized (*S*)-BIPHEMP, −40 °C, 2 equiv of PMHS and *t*-AmOH. [g] $CuCl_2 \cdot 2H_2O$ (5 mol %), *t*-BuONa (20 mol %), (*S*)-*p*-tolBINAP (5 mol %), PMHS (4 equiv), EtOH (4 equiv), toluene/THF (50/50), 0 °C. [h] 1 h was required for 100% conversion.

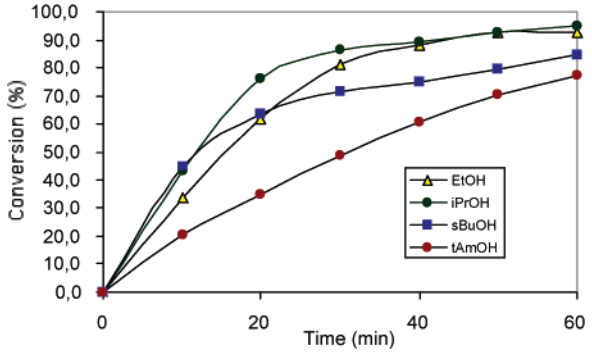


Figure 2. Reduction of **18** in the presence of various alcohol additives

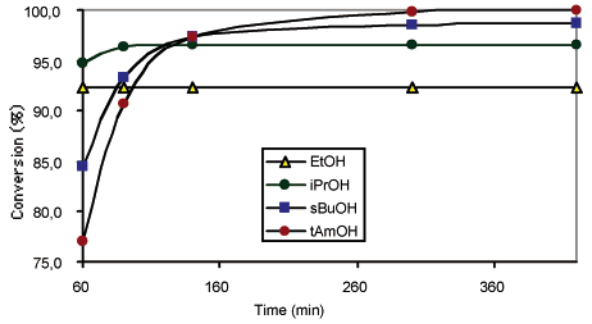


Figure 3. Reduction of **18** after complete addition of alcohols.

%), and PMHS (4 equiv) in *c*-hexane. While EtOH and *i*-PrOH accelerate the reduction to similar degrees, the reduction with 3-pentanol is slightly slower and is significantly slower with *t*-AmOH (Figure 2).

When the degree of conversion to product was monitored after the 60 min alcohol-addition time, the reaction with EtOH showed no further progress (Figure 3). With *i*-PrOH, the reaction continued from 95% conversion at 60 min to 97% after 90 min, and then proceeded no further. With 3-pentanol, the reduction proceeds from 85% conversion after 60 min to 99% after 300 min. With *t*-AmOH, the reaction proceeded from 77% at 60 min to 100% conversion after ~300 min.

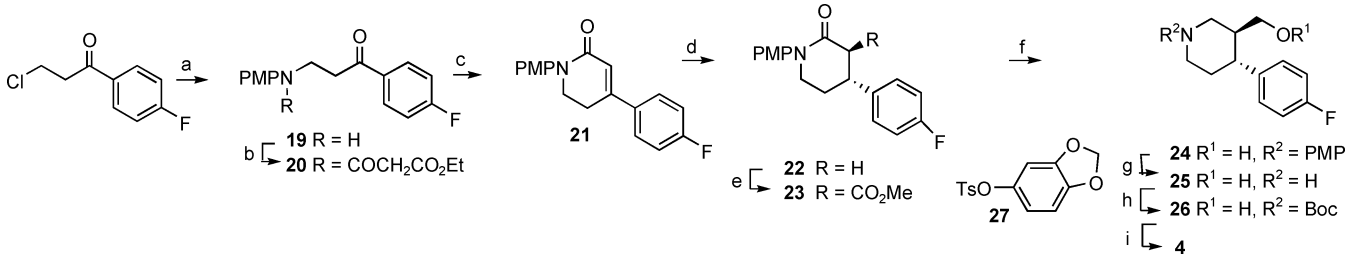
We have applied this methodology to a catalytic enantioselective synthesis of **4**, which is outlined in Scheme 3. *p*-Anisidine and 4-fluoro-3′-chloropropiophenone were mixed with triethylamine in refluxing THF to afford **19** in 77% yield. The crude amidation product **20** was dissolved in an ethanolic solution of NaOEt. After being refluxed for 30 min, the mixture was added to cold water, from which lactam **21** was isolated in 76% yield after filtration and azeotropic removal of residual water. ^{1}H NMR analysis revealed a 20:1 mixture of the desired product and the β,γ-unsaturated isomer. The reduction of **21** was considerably slower than other lactams, with ~20% conversion being realized after 18 h. In an ongoing investigation, a further acceleration in the conjugate reductions has been noted when the reactions are performed open to the atmosphere.[21] We were gratified to find that running the reaction in air and use of 16 equiv each of PMHS and *t*-AmOH allowed for **22** to be isolated in 90% yield and 90% ee with as little as 0.5 mol % (*R*)-*p*-tolBINAP.[22]

This intermediate was converted to **24** in two steps (81% overall yield) using previously reported conditions for a similar substrate.[2c] Because of complications with the oxidative removal of the PMP functionality in the presence of a second electron-rich aromatic ring, a protecting group switch to Boc was performed, affording **26** in 75% yield over two steps.

During the course of ongoing efforts to develop transition metal-catalyzed methods for coupling alcohols with aryl tosylates,[23] control experiments revealed that heating primary alcohols and aryltosylates in the presence of a base afforded

(21) Hughes, G.; Buchwald, S. L., unpublished results. For related effects in catalytic enantioselective copper-hydride reductions of ketones, see: Sirol, S.; Courarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111.
(22) We have noted that a larger excess of alcohol and silane is required in the air-accelerated reactions as the alcohol silylation side reaction appears to be accelerated more dramatically than conjugate reduction by the presence of air. This effect is less pronounced with larger alcohols such as *t*-AmOH than it is with smaller ones such as EtOH. In air, optimal rates and conversions are achieved with 5 equiv of $CuCl_2$ and 10 equiv of *t*-BuONa per ligand, whereas an excess of Cu and base per ligand under anaerobic conditions was found to give poor conversions.
(23) Huang, X.; Buchwald, S. L., unpublished results.

Scheme 3. Synthesis of (−)-Paroxetine[a]



[a] (a) $PMPNH_2$(1.1 equiv), Et_3N (1.2 equiv), THF, reflux, 75%. (b) $ClCOCH_2CO_2Et$ (1.1 equiv), Na_2CO_3 (sat), CH_2Cl_2. (c) NaOEt (4 equiv), EtOH, reflux, 74% (two steps). (d) PMHS (16 equiv), *t*-AmOH (16 equiv), (*S*)-*p*-tol-BINAP (0.5 mol %), $CuCl_2$ (2.5 mol %), *t*-BuONa (5 mol %), C_6H_5F, air, 23 °C 90%, 90% ee. (e) NaH (6 equiv), MeOH (3 equiv), $(MeO)_2CO$ (3 equiv), toluene, reflux, 86%. (f) BH_3·THF, reflux, 97%. (g) CAN (4 equiv), CH_3CN/H_2O (3/1). (h) Boc_2O (2.0 equiv), NaOH (1.5 equiv), toluene, H_2O, 75% (two steps). (i) (1) **27** (1.3 equiv), Cs_2CO_3 (1.5 equiv), xylene, 130 °C; (2) TFA/CH_2Cl_2, 52% (two steps).

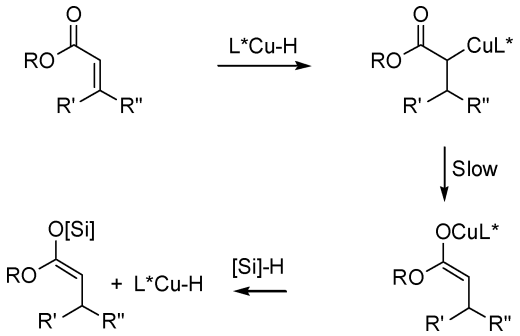


Figure 4. Rationale for the acceleratory effect of alcohol additives.

aryl ethers in the absence of metallic catalysts.[24] Thus, treating **26** with tosylate **27** in the presence of Cs_2CO_3 at 130 °C in xylene afforded the desired aryl ether. Removal of the Boc group afforded **4** in 52% yield from **26**.

Discussion

It was found that the rate of the conjugate reduction was dramatically accelerated upon inclusion of alcohol additives. If the slow step in the absence of alcohols were σ-bond metathesis, this would suggest that the silylation of copper alkoxides is much faster than the silylation of copper enolates. As there seems to be no obvious steric or electronic basis for this acceleration, we speculate that the sluggishness of the enolate silylation might be the result of a preference for C-bound versus O-bound copper enolate (Figure 4). One might expect that the C-bound tautomor would be impervious to σ-bond metathesis, requiring conversion to the O-enolate prior to catalyst turnover. The addition of alcohols alleviates this problem by protonating the enolate to give an alkoxide that readily undergoes σ-bond metathesis.

We also observed that the rate of reduction is dependent on the size of the alcohol additive. While EtOH and *i*-PrOH give rise to similar rates, the use of larger alcohols (*s*-BuOH and particularly *t*-AmOH) results in progressively slower reaction rates. This suggests that, at least with larger alcohols, the rate-limiting step is either protonation of the copper enolate or σ-bond metathesis. A modest k_H/k_D of 1.8 was observed when the conjugate reductions were performed with *t*-AmOH versus *t*-AmOD; however, this result is difficult to interpret. While the enolate protonation step is expected to be slower with *t*-AmOD, the protonation of the copper-hydride catalyst (leading to alcohol silylation) should also be slower. As a result, one might expect to see a higher concentration of the active catalyst and hence a faster reaction which would counteract the hindrance in the enolate protonation step. It is also possible that the rates of protonation of σ-bond metathesis are similar. A more detailed kinetic study will be required to distinguish between these possibilities.

We attribute the fact that higher conversions are realized with larger alcohols to the rate of alcohol silylation being hampered to a greater extent than the rate of conjugate reduction by an increase in the size of the alcohol.

Conclusion

In conclusion, we have developed a conjugate reduction protocol that allows for the catalytic enantioselective formation of five- and six-membered lactones and lactams possessing a β-stereocenter. The addition of alcoholic additives was found to be crucial for higher yields of the desired products. In addition to improved yields, a dramatic increase in the reaction rate was also observed. Finally, we have applied this methodology to a brief, catalytic enantioselective approach to (−)-Paroxetine.

Experimental Section

The following are representative procedures for conjugate reduction. A full account of the reaction conditions and characterization of substrates and products can be found in the Supporting Information.

4-Butyldihydrofuran-2-one. $CuCl_2·2H_2O$ (4.8 mg, 0.036 mmol, 5 mol %), (*S*)-p-tolBINAP (24.2 mg, 0.0356 mmol, 5 mol %), and *t*-BuONa (14.0 mg, 0.143 mmol, 20 mol %) were added to a Schlenk tube which was then evacuated and charged with an argon atmosphere. PMHS (171 μL, 2.85 mmol, 4 equiv) and pentane (1.0 mL) were added, and the mixture was stirred for 2 h before cooling to −20 °C. A solution of **10a** (100 mg, 0.713 mmol, 1 equiv), dodecane (100 μL), and *i*-PrOH (220 μL, 2.85 mmol, 4 equiv) in toluene (1.0 mL) was added via syringe. After 3 h, GC analysis showed complete conversion, and the mixture was partitioned between 10% HCl and ethyl acetate. The aqueous layer was extracted two times with fresh portions of ethyl acetate, and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (15 → 20% ethyl acetate/hexanes) to afford the title compound as a colorless oil (90 mg, 89% yield). Chiral GC analysis (GTA column, 1 mL/min, 90 °C, 60 min, then 1 °C/min to 120 °C, hold for 20 min, retention times: 93.9 min (major), 95.5 min (minor)) showed 86% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7 Hz, 3H), 1.23−1.41 (m, 4H), 1.44−1.54 (m, 2H), 2.19 (dd, J = 16.5, 7.5 Hz, 1H), 2.46−2.68 (m, 2H), 3.93 (ABX, dd, J =

(24) We presume that tosyl transfer occurs between **26** and **27** to produce a primary tosylate and a phenol. In the presence of base, the phenol displaces the primary tosylate to afford the desired coupling product. For similar examples of transfer of activation, see: (a) Sobolov, S. B.; Sun, J.; Cooper, B. A. *Tetrahedron Lett.* **1998**, *39*, 5685. (b) Kim, T. H.; Lee, G.-J. *J. Org. Chem.* **1999**, *65*, 2941.

9, 7 Hz, 1H), 4.42 (ABX, dd, J = 9, 7, Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.06, 22.71, 29.67, 32.95, 34.70, 35.86, 73.61, 177.49. α_D (589 nm, 38.5 mg/mL $CHCl_3$) = +5.[25]

(4*S*)-4-Propyltetrahydropyran-2-one. $CuCl_2 \cdot 2H_2O$ (4.8 mg, 0.036 mmol, 5 mol %), (*S*)-BIPHEMP (24.2 mg, 0.0356 mmol, 5 mol %), and *t*-BuONa (14.0 mg, 0.143 mmol, 20 mol %) were added to a Schlenk tube which was then evacuated and charged with an argon atmosphere. PMHS (86 μL, 1.426 mmol, 2 equiv) and toluene (0.5 mL) were added via syringe, and the mixture was stirred for 30 min. Pentane (1 mL) was added, and the mixture was cooled to −40 °C. A solution of **12a** (100 mg, 0.713 mmol, 1 equiv) and dodecane (100 μL) in toluene (0.5 mL) was added via syringe, followed by *t*-AmOH (156 μL, 1.43 mmol, 2 equiv). After 3 h, GC analysis showed complete conversion, and the reaction was quenched by the addition of 10% hydrochloric acid. The aqueous layer was extracted three times with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography (25% ethyl acetate/hexanes) afforded a mixture of the title compound and an unidentified byproduct. A second flash chromatography (80% ether/hexanes) afforded the title compound as a colorless liquid (71 mg, 70% yield). Chiral GC analysis (GTA column, 1 mL/min, 120 °C, 50 min, retention times: 41.3 min (major), 46.2 min (minor)) showed 86% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88−1.00 (m, 3H), 1.29−1.42 (m, 4H), 1.44−1.60 (m, 1H), 1.90−2.04 (m, 2H), 2.14 (ABX, dd, J = 17, 10 Hz, 1H), 2.70 (ABX, ddd, J = 17, 4, 1.5 Hz, 1H), 4.26 (ABX, ddd, J = 11, 10, 3.5, 1H), 4.42 (ABX, ddd, J = 11, 5, 4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 14.16, 19.72, 29.06, 31.37, 36.74, 38.51, 68.78, 171.76. α_D (589 nm, 23.8 mg/mL $CHCl_3$) = −21.4.[26]

(4*R*)-4-Methyl-1-(4-methoxyphenyl)pyrrolidin-2-one. A solution of **13** (50 mg, 0.267 mmol, 1 equiv) and *i*-PrOH (82 μL, 1.1 mmol, 4 equiv) in THF (0.50 mL) was added to a 0 °C slurry of $CuCl_2 \cdot 2H_2O$ (1.8 mg, 0.013 mmol, 5 mol %), (*S*)-*p*-tol-BINAP (9.1 mg, 0.013 mmol, 5 mol %), *t*-BuONa (5.2 mg, 0.053 mmol, 20 mol %), and PMHS (64 μL, 1.1 mmol, 4 equiv) in *c*-hexane (0.50 mL). The mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 10% hydrochloric acid, and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography (70% ethyl acetate/hexanes) afforded the title compound as a white crystalline solid (48 mg, 95%). Chiral HPLC analysis (Daicel Chiralpak OB-H column (0.46 cmØ × 25 cm), 0.5 mL/min, 40% *i*-PrOH/hexane, 254, 280 nm, retention times: 18.4 min (major), 24.4 min (minor)) showed 93% ee. mp (CH_2Cl_2): 49−51 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (d, J = 6.8 Hz, 3H), 2.22 (ABX, dd, J = 16.7, 7.4 Hz, 1H), 2.55 (hextet, J = 7.4 Hz, 1H), 2.72 (ABX, dd, J = 16.7, 8.4 Hz, 1H), 3.41 (ABX, dd, J = 9.4, 6.4 Hz, 1H), 3.90 (ABX, dd, J = 9.4, 7.6 Hz, 1H), 6.89 (ABX, dm, J = 9.1 Hz, 2H), 7.47 (ABX, J = 9.1 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 19.42, 26.25, 40.61, 55.36, 56.26, 113.91, 121.72, 132.47, 156.43, 173.49. IR (film, cm^{-1}): 1688, 1513, 1397, 1266, 1034. Elemental analysis: %C (calc.) = 70.22, %C (found) = 70.06, %H (calc.) = 7.37, %H (found) = 7.31. α_D (589 nm, 23.8 mg/mL $CHCl_3$) = −4.2.

(4*R*)-4-(4-Fluorophenyl)-1-(4-methoxyphenyl)piperidin-2-one (22). $CuCl_2$ (13.3 mg, 0.0992 mmol, 2.5 mol %) and *t*-BuONa (19.1 mg, 0.198 mmol, 5 mol %) were added to a mixture of **21** (1.18 g, 3.97 mmol, 1.0 equiv), (*R*)-*p*-tolBINAP (13.5 mg, 0.0198 mmol, 0.5 mol %), PMHS (3.81 mL, 63.5 mmol, 16 equiv), and *t*-AmOH (6.95 mL, 63.5 mmol, 16 equiv) in fluorobenzene (8 mL). After 45 min, 10% hydrochloric acid was added, and the mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (60% → 100% ethyl acetate/hexanes) to afford the title compound as a crystalline solid (1.00 g, 89%, based on 95% pure starting material). Chiral HPLC analysis (Daicel Chiralpak OD column (0.46 cmØ × 25 cm), 1.0 mL/min, 25% *i*-PrOH/hexane, retention times: 19.4 min (minor), 22.3 min (major)) showed 90% ee. mp (Et_2O): 183−186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.02−2.27 (m, 2H), 2.64 (ABX, dd, J = 17, 11 Hz, 1H), 2.86 (ABX, ddd, J = 17, 5, 2 Hz, 1H), 3.18−3.30 (m, 1H), 6.62 (ABX, ddd, J = 12, 5, 4 Hz, 1H), 3.68−3.83 (m, 1H), 3.80 (s, 3H), 6.92 (ABX, dt, J = 9, 2 Hz, 2H), 7.03 (tt, J = 9, 2 Hz, 2H), 7.16 (AB, dt, J = 9, 2 Hz, 2H), 7.21 (ABX, dd, J = 9, 5.5 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 30.98, 38.31, 40.21, 51.06, 55.64, 114.61, 115.65 (d, J = 19 Hz, 2C), 127.41, 128.01 (d, J = 8 Hz, 2C), 135.74, 139.08 (d, J = 3 Hz, 2C), 158.19, 161.60 (d, J = 244 Hz, 2C), 169.16. IR (neat film, cm^{-1}): 1642, 1511, 1266. Elemental analysis: %C (calc.) = 72.22, %C (found) = 72.22, %H (calc.) = 6.06, %H (found) = 6.05. α_D (589 nm, 12.8 mg/mL $CHCl_3$) = +8.

Acknowledgment. We thank the National Institutes of Health (GM 46059) for funding and Pfizer, Merck, and Bristol-Myers Squibb for additional unrestricted support. G.H. thanks the Natural Sciences and Engineering Research Council (NSERC) of Canada for a postdoctoral fellowship. We are grateful to Dr. Rudy Schmid (Roche) for a generous gift of (*S*)-BIPHEMP. We also thank Prof. Jeff Stryker for helpful comments.

Supporting Information Available: Preparation and characterization of all substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0351692

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