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Asymmetric Conjugate Addition of Grignard Reagents to Pyranones

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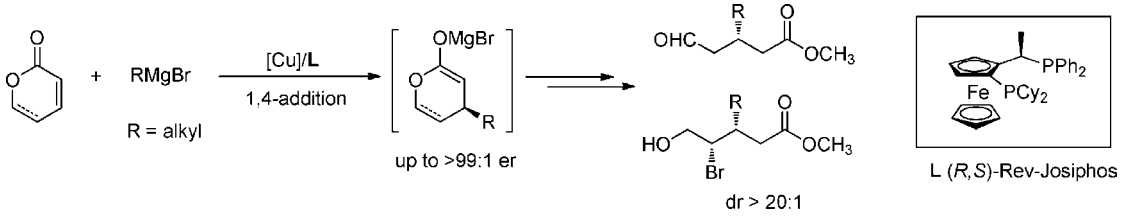
ABSTRACT



An efficient enantioselective synthesis of lactones was developed based on the catalytic asymmetric conjugate addition (ACA) of alkyl Grignard reagents to pyranones. The use of 2*H*-pyran-2-one for the first time in the ACA with Grignard reagents allows for a variety of further transformations to access highly versatile building blocks such as β-alkyl substituted aldehydes or β-bromo-γ-alkyl substituted alcohols with excellent regio- and stereoselectivity.

3,4-Dihydropyran-2-ones and their derivatives have attracted major attention due to the interesting biological activities[1] and the synthetic perspective[2] associated with these privileged structures. In recent years, a number of approaches have been reported toward the preparation of chiral 3,4-dihydropyran-2-ones.[3]

A concise route for the enantioselective synthesis of enol lactones through Michael addition followed by cyclization using sequential catalytic conditions has been described by Kanemasa et al.[3a] Moreover, chiral N-heterocyclic carbene (NHC) catalyzed oxo-diene Diels–Alder reactions of α-chloroaldehydes have been successfully applied by the group of Bode to afford the trisubstituted dihydropyran-2-ones in a stereoselective manner.[3b,c] Mukaiyama and coworkers[3d,e] reported the organocatalytic conversion of silyl enolates and α,β-unsaturated ketones into the optically active 3,4-dihydropyran-2-ones employing cinchona alkaloid derived chiral quaternary ammonium phenoxides.

Slower to develop, however, have been protocols that allow the introduction of alkyl groups at the newly formed stereogenic center in the structurally diverse 3,4-dihydropyran-2-ones. While addressing this challenge, we envisioned the possibility of applying 2*H*-pyran-2-ones[4] together with alkyl Grignard reagents to access optically active dihydropyran-2-ones via

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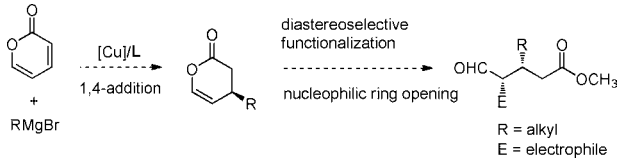
the copper-catalyzed asymmetric conjugate addition (ACA) reaction.[5] 2*H*-Pyran-2-ones featuring electron deficient diene moieties are common precursors for [4 + 2] and [2 + 2] cycloadditions to construct bicyclic building blocks.[6] However, the increased electron delocalization, compared with acyclic α,β-unsaturated esters, results in a lower reactivity toward ACA reactions.[7] To the best of our knowledge, asymmetric 1,4-addition of Grignard reagents to 2*H*-pyran-2-ones still remain elusive. Such a reaction could provide an efficient, direct, and versatile method toward the synthesis of chiral 3,4-dihydropyran-2-ones. In addition, the resulting chiral intermediates would allow for a variety of further transformations in particular by addition to the enol ester moiety to access highly versatile intermediates with excellent regio- and stereochemical control (Scheme 1).

Scheme 1. Catalytic Asymmetric 1,4-Addition and Proposed Routes to Chiral Intermediates by Further Transformation of Dihydropyran-2-ones



Extensive efforts have been made to develop efficient catalysts for the copper-catalyzed asymmetric conjugate addition (ACA) of Grignard reagents to acyclic α,β-unsaturated compounds.[5,8] The copper-catalyzed ACA reaction of Grignard reagents to cyclic enones has also been successfully achieved with excellent enantioselectivities by several groups.[9] However, despite wide scope, this method still presents limitations using less reactive substrates such as simple cyclic α,β-unsaturated esters, providing lactones only with moderate enantioselectivity.[9a,e]

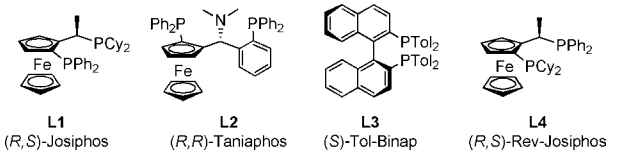


Figure 1. Chiral diphosphine ligands for copper-catalyzed asymmetric conjugate addition.

Inspired by our recent study of the Cu-catalyzed ACA reaction of Grignard reagents to coumarins,[10] we present here the Cu-catalyzed conjugate addition of Grignard reagents to 2*H*-pyran-2-ones by using ferrocenyl-based bisphosphine ligands (Figure 1), providing the regio- and enantioselective synthesis of 3,4-dihydropyran-2-ones.

We began our studies by examining the conjugate addition of ethylmagnesium bromide to 2*H*-pyran-2-one in the presence of $CuBr \cdot SMe_2$ and (R_{Fe},*S*)-Josiphos **L1** at −80 °C in CH_2Cl_2 (Table 1, entry 1). Although potential competing pathways for 2*H*-pyran-2-one include 1,6-conjugate addition[7,11] and 1,2-addition, exclusive formation of 1,4-addition product with moderate enantioselectivity was observed in the preliminary experiments. When we turned our attention to (R_{Fe},*R*)-Taniaphos ligand **L2**, which has been successfully employed in the conjugate addition of Grignard reagents to cyclic enones,[9a] **2a** was obtained only as a racemic product. Additionally, ligand **L3** ((*S*)-Tol-Binap) also provided **2a** with low level of enantioselectivity (55:45 er). In contrast, a promising enantiomeric ratio (86:14 er) was obtained with full conversion using commercially available reverse-Josiphos ligand **L4** (Table 1, entry 4).[12]

Encouraged by the initial screening, general experimental parameters including solvent and temperature were examined with respect to yield and regio- and enantioselectivity. It is important to note that the use of *t*-BuOMe as solvent is essential to yield the product in a highly enantioselective fashion. A slight increase in temperature (−72 °C) led to full conversion and an enhancement of enantiomeric ratio to 95:5 (Table 1, entry 8). Different copper(I) salts in combination with ligand **L4** were also

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(9) For selected examples of copper-catalyzed ACA reaction of Grignard reagents to cyclic enones, see: (a) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834. (b) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (c) Matsumoto, Y.; Yamada, K.-I.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578. (d) Robert, T.; Velder, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7718. (e) Naeemi, Q.; Robert, T.; Kranz, D. P.; Velder, J.; Schmalz, H.-G. *Tetrahedron: Asymmetry* **2011**, *22*, 887.

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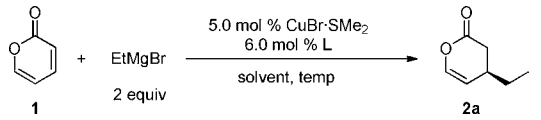
(12) The opposite enantiomer of ligand **L4** is also commercially available.

Table 1. Screening of Reaction Parameters[a]



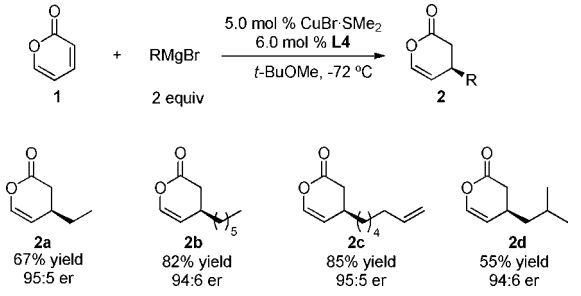
entry	ligand	solvent	temp (°C)	yield[b] (%)	er[c]
1[d]	**L1**	CH_2Cl_2	−80	54	69:31
2[d]	**L2**	CH_2Cl_2	−80	36	50:50
3[d]	**L3**	CH_2Cl_2	−80	40	55:45
4[d]	**L4**	CH_2Cl_2	−80	63	86:14
5	**L4**	CH_2Cl_2	−80	65	88:12
6[f]	**L4**	Et_2O	−80	nd[e]	71:29
7	**L4**	*t*-BuOMe	−80	38[g]	92:8
8	**L4**	*t*-BuOMe	−72	67	95:5

[a] Formation of 1,6- or 1,2-addition product was not observed unless otherwise noted. General conditions for ACA: 5.0 mol % of $CuBr \cdot SMe_2$, 6.0 mol % of ligand, 2 equiv of RMgBr in 7 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 2.5 mL of CH_2Cl_2. [e] nd = not determined. [f] 1,2-Addition product was obtained. [g] Full conversion was not achieved.

investigated. It turned out that the use of a copper halide was essential in terms of conversion (see the Supporting Information, Table S1). As reflected by this screening, $CuBr \cdot SMe_2$ was still the most effective copper(I) salt for further studies (Table 1, entry 8).

With the optimized reaction conditions established, we then directed our efforts toward expanding the scope of Grignard reagents. By employing linear hexylmagnesium reagent as nucleophile, product **2b** was obtained in 82% yield with 94:6 er (Scheme 2). In addition, the reaction could be carried out at 3.0 mmol scale to afford the similar result. Functionalized Grignard reagents bearing a terminal alkene moiety also work well to afford the corresponding product **2c** in 95:5 er. Moreover, addition of branched Grignard reagent (R = *i*-Bu) provided the desired product in good enantiomeric ratio (95:5 er) (**2d**, Scheme 2).[13]

Scheme 2. Screening of Grignard Reagents[a]

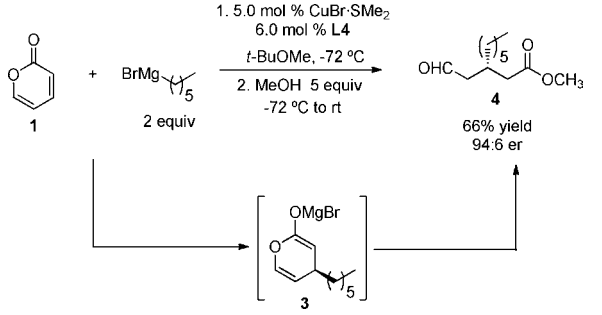


[a] General conditions for ACA: 5.0 mol % of $CuBr \cdot SMe_2$, 6.0 mol % of **L4**, 2 equiv of RMgBr in 7 mL *t*-BuOMe at −72 °C. Isolated yields. Enantiomeric ratio of product **2** was determined by chiral HPLC analysis.

(13) A decrease in yield was attributed to the volatility of product.

With an effective method for Cu-catalyzed conjugate addition to 2*H*-pyran-2-one in hand, we turned our attention to explore the reactivity of the chiral magnesium enolate **3**, which could be further converted *in situ* to more advanced chiral building blocks (Scheme 3).[8f,10,14] 2*H*-Pyran-2-one **1** was treated with hexylmagnesium bromide under the optimized conditions, followed by quenching the resulting enolate **3** with MeOH (5 equiv) at −72 °C. After warming to room temperature, β-substituted aldehyde **4**, bearing an ester group, was isolated in 66% yield and 94:6 er. The formation of product **4** is presumably due to protonation of intermediate **3** followed by transesterification. It should be noted that it is highly challenging to achieve β-substituted aldehydes by performing the direct asymmetric conjugate addition with organometallic reagents to substrates such as α,β-unsaturated aldehydes or β,γ-unsaturated-α-ketoesters.[15] The present transformation reveals a valuable alternative upon which to design the stereoselective synthesis of highly functionalized β-substituted aldehydes in a concise manner.

Scheme 3. Trapping/Ring-Opening Reaction of Magnesium Enolate



Although strategies have been introduced for the asymmetric α-bromination of aldehydes based upon organocatalysis,[16] to date, there is no example for the synthesis of optically enriched α-bromoaldehyde through a cascade protocol involving organometallic reagents. Here we envisioned that the resulted 3,4-dihydro-pyran-2-ones **2** are potential synthons to produce α,β-substituted aldehydes through diastereoselective α-bromination. Enantioenriched product **2b** was first treated with NBS for the bromination catalyzed by NH_4OAc[17] in MeOH to afford

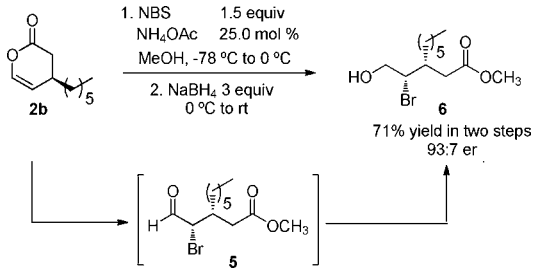
(14) For the synthetic utility of magnesium enolates, see: Galeštoková, Z.; Šebesta, R. *Eur. J. Org. Chem.* **2011**, *2011*, 7092.

(15) (a) Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2010**, *132*, 13152. (b) Palais, L.; Babel, L.; Quintard, A.; Belot, S. b.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988. (c) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794.

(16) For reviews on the enantioselective α-bromination, see: (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (b) Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005. For representative examples, see: (c) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jorgensen, K. A. *Chem. Commun.* **2005**, 4821. (d) Kano, T.; Shirozu, F.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 7590.

(17) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470.

Scheme 4. α-Bromination of **2b** Followed by Reduction

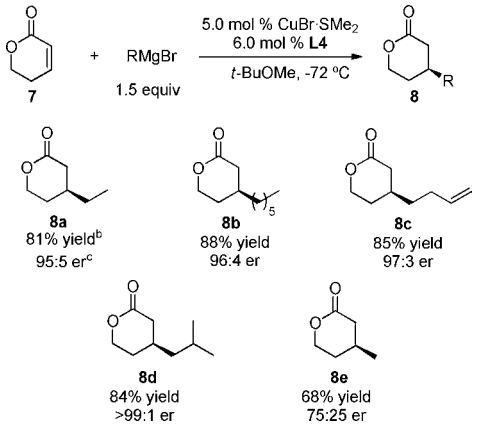


α-bromoaldehyde **5** in a completely diastereoselective fashion (Scheme 4). Because of instability problems,[16c] the intermediate **5** was then instantly treated with $NaBH_4$ (3 equiv) at 0 °C to provide the corresponding alcohol **6** in 71% yield and high enantiomeric ratio (93:7 er). The relative configuration of product **6** was assigned on the basis of ^1H NMR and NOESY analysis. The stereochemical outcome is attributed to the stereoinduction of new stereogenic carbon center formed in the copper-catalyzed ACA reaction.

We decided also to examine the application of our catalytic protocol to the copper-catalyzed ACA of Grignard reagents to 5,6-dihydro-2*H*-pyran-2-one (Scheme 5). Although examples of this conjugate addition have been reported,[9a,e,18,19] high loading of chiral ligands[18] or reduced enantioselectivity[9a,e] frequently imposed limitation on this protocol. To our delight, the present catalytic system of reversed-Josiphos **L4**/ $CuBr \cdot SMe_2$ is highly versatile in the ACA reaction of Grignard reagents to yield products **8** with excellent enantioselectivity (up to >99:1 er) (Scheme 5).

Representative results with various Grignard reagents are summarized in Scheme 5. When substrate **7** was subjected to ACA conditions using EtMgBr identical to those used for reactions of 2*H*-pyran-2-one **1**, the desired 1,4-addition product **8a** was obtained with high yield (81%) and excellent enantiomeric ratio (95:5 er). Noteworthy, the relative amount of Grignard reagents could be reduced from 2.0 to 1.5 equiv, possibly due to the higher reactivity of lactone **7**. Transformations with Grignard reagents bearing longer alkyl chains proceeded to afford the optically active esters **8b** and **8c** in 88% and 85% yield with 96:4 and 97:3 er, respectively (Scheme 5). Remarkably, in the case of the branched Grignard reagent (R = *i*-Bu), the desired

Scheme 5. Copper-Catalyzed ACA of Grignard Reagents to 5,6-Dihydro-2*H*-pyran-2-one[a]



[a] General conditions for ACA: 5.0 mol % of $CuBr \cdot SMe_2$, 6.0 mol % of **L4**, 1.5 equiv of RMgBr in 7 mL of *t*-BuOMe at −72 °C. [b] Isolated yield. [c] Enantiomeric ratios of products were determined by chiral GC analysis.

product **8d** was obtained as a single enantiomer (>99:1 er). The copper-catalyzed ACA of less reactive methylmagnesium bromide proceeded also, although this transformation showed lower enantioselectivity (Scheme 5).

In summary, we have developed a highly efficient enantioselective synthesis of structurally diverse lactones based on the asymmetric conjugate addition of Grignard reagents to 2*H*-pyran-2-one and 5,6-dihydro-2*H*-pyran-2-one. The synthetic applicability of the products from this catalytic C−C bond formation is demonstrated in the stereoselective synthesis of an optically active β-alkyl substituted aldehyde and a β-bromo-γ-alkyl substituted alcohol, which are valuable chiral multifunctional synthons.

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

The authors declare no competing financial interest.

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