Asymmetric Addition of Organolithium Reagents to Prochiral Arene Tricarbonylchromium Complexes

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The external ligand-controlled enantioselective addition of organometallic reagents to prochiral molecules is a powerful tool in asymmetric methodology. Previous work in this area has centered on 1,2-additions to aldehydes and aldeheyde imines and on 1,4-additions to α,β-unsaturated carbonyl compounds.[1] Tomioka, Shindo, and Koga have reported highly enantioselective organolithium addition/protonation reactions with cyclohexylimines derived from 1-naphthaldehyde and, more recently, with 1-naphthyl esters.[2] However, methods of asymmetric C−C bond formation in the transformation of benzene and substituted benzenes remain scarce[3] despite the obvious synthetic potential of the transformation of an arene into a chiral nonracemic alicyclic compound.

The present investigation is based on our finding that the consecutive addition of a C-nucleophile and a C-electrophile to an arene complexed to the electrophilic $Cr(CO)_3$ moiety[4] gives 1,2-*trans*-disubstituted dihydroarenes.[5] More recently, we have shown that such transformations can be combined with *ortho*-regioselectivtiy for the nucleophile addition by the use of appropriate N-containing auxiliaries σ-bound to the arene ring[6] (Scheme 1). High diastereoselectivity was observed in this sequence when enantiomerically pure tricarbonyl phenyloxazoline chromium complexes were used.[7]

Here we report our initial results on the alternative approach of regio- and enantioselective additions of alkyl-, vinyl-, and aryllithium reagents to two prochiral arene $Cr(CO)_3$ complexes in the presence of chiral ligands.

Four chiral ligands figure in our investigation of the sequential addition of phenyl-, vinyl-, and alkyllithium reagents and propargyl bromide to the phenyloxazoline complex **1** to give the chiral nonracemic cyclohexadiene **2** (Table 1). They are either commercially available or readily synthesized.[8,9] Racemic products were obtained when using (−)-sparteine ((−)-**3**) in either THF or diethyl ether, indicating insufficient ligand complexation and/or rapid background reaction. All subsequent reactions were carried out in toluene. In this solvent the background reaction—addition in the absence of added ligand—is negligibly small at −78 °C. The results are

Scheme 1

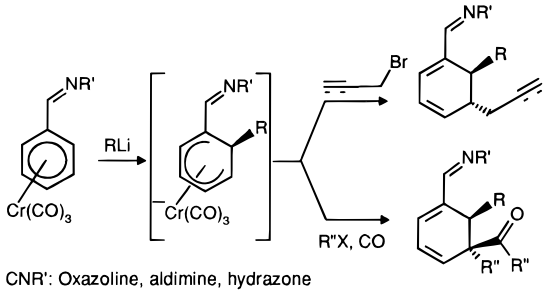
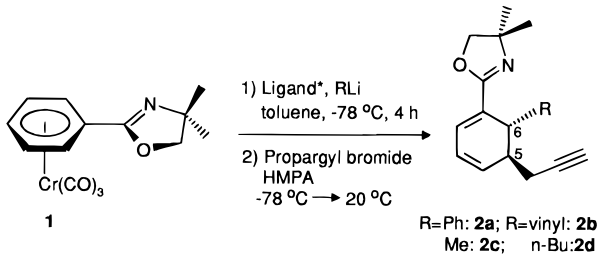
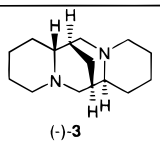
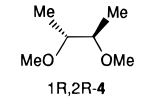
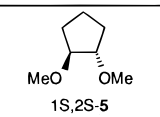
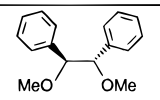


Table 1. Sequential Asymmetric Addition of RLi/L* and Propargyl Bromide to Complex



Entry	RLi[a]	Ligand*[b]	Product (Yield, %)[c]	Config.[d]	ee[e] (%)
1	PhLi[f]	 (-)-**3**	(+)-**2a** (72)	5*S*,6*S*	54
2	VinylLi[g]		(+)-**2b** (87)	5*S*,6*R*	34
3	MeLi[h]		(+)-**2c** (70)	5*S*,6*R*	47
4	n-BuLi[i]		(+)-**2d** (65)[j]	5*S*,6*R*	36
5	PhLi[f]	 1R,2R-**4**	(-)-**2a** (72)	5*R*,6*R*	81
6	VinylLi[g]		(-)-**2b** (85)	5*R*,6*S*	50
7	MeLi[h]		(-)-**2c** (60)	5*R*,6*S*	47
8	n-BuLi[i]		(-)-**2d** (68)	5*R*,6*S*	45
9	PhLi[f]	 1S,2S-**5**	(+)-**2a** (66)	5*S*,6*S*	81
10	VinylLi[g]		(+)-**2b** (60)	5*S*,6*R*	61
11	MeLi[h]		(+)-**2c** (50)	5*S*,6*R*	84
12	n-BuLi[i]		(+)-**2d** (75)	5*S*,6*R*	61
13	PhLi[f]	 1S,2S-**6**	(+)-**2a** (66)	5*S*,6*S*	93[k]
14	VinylLi[g]		(+)-**2b** (53)	5*S*,6*R*	87
15	MeLi[h]		(+)-**2c** (51)	5*S*,6*R*	87
16	n-BuLi[i]		(+)-**2d** (67)	5*S*,6*R*	65

[a] RLi was added to a solution of complex **1** and the chiral ligand. Control experiments in which RLi and the chiral ligand were mixed prior to addition to a solution of complex **1** gave very similar results (yield, ee). [b] Two equiv of chiral ligand was used. [c] Yield of isolated product after flash chromatography. [d] The absolute configuration is based on that established for **2a**. This was done after conversion to the SAMP-hydrazone derivative by comparison of the sign of optical rotation with that of an analogously converted compound whose configuration is known from an X-ray structure (see ref 7). [e] Determined by chiral HPLC-analysis (Chiralcel OD: e.g., **2d**, hexane/*i*-PrOH = 200/1, 1 mL/min, retention time; (5*R*,6*S*)-(−)-**2d**, 7.8 min; (5*S*,6*R*)-(+)-2d, 9.9 min) and by optical rotation. fAdded as a diethyl ether solution. [g] Prepared from tetravinyltin and MeLi in THF and used as toluene solution after removal of THF *in vacuo*. [h] Added as a cyclohexane/diethyl ether (70/30) solution. [i] Added as a hexane solution. [j] In the absence of HMPA **2d** was obtained in a yield of 25% with an ee of 36%. [k] $[\alpha]^{20}_D = +479$ ($CHCl_3$, $c = 0.4$).

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(1) For reviews see: (a) Tomioka, K. *Synthesis* **1990**, 541. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, 92, 771. For recent reports of additions to imines see: (c) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. (d) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429.

(2) (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (b) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681.

(3) Birch reduction/alkylation of benzoic acid derivatives: For a review see (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1. For chiral examples see: (b) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828 and references cited therein.

(4) For a review of nucleophilic additions to (arene)$Cr(CO)_3$ complexes see: Semmelhack, M. F. In *Comprehensive Organometallic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, p 517.

(5) (a) Kündig, E. P.; Cunningham, A. F., Jr.; Paglia, P.; Simmons, D. P. *Helv. Chim. Acta* **1990**, *73*, 386. (b) Kündig, E. P.; Inage, M.; Bernadinelli, G. *Organometallics* **1991**, *10*, 2921.

(6) Kündig, E. P.; Ripa, A.; Liu, R.; Bernardinelli, G. *J. Org. Chem.* **1994**, *59*, 4773.

(7) Kündig, E. P.; Ripa, A.; Bernardinelli, G. *Angew. Chem., Intl. Ed. Engl.* **1992**, *31*, 1071.

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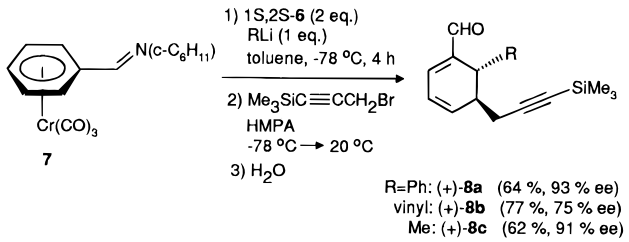
summarized in Table 1. The product yields achieved using these conditions are comparable to those we obtain for the achiral version where the reaction is carried out in THF.[6] For the second step of the sequence, the reaction with propargyl bromide, addition of HMPA (10 equiv) is required as previously noted in the achiral reaction. In its absence the yield was greatly reduced (e.g., entry 4, from 65 to 25%).

In all reactions studied so far, a significant degree of enantioselectivity has been obtained, along with the already established regio- and stereoselectivity. An asymmetric double addition to a benzene-based ring system has been achieved, and the reaction exhibits a high degree of control in the creation of the two new stereogenic centers. The addition of the nucleophile, under the influence of the external chiral ligand, preferentially occurs at one of the enantiotopic *ortho* positions of the arene.[10] As expected, reactions using **4** as the external ligand resulted in excesses of the opposite enantiomer to that obtained when using **5** or **6**.

In general, the reactions in which PhLi is the nucleophile result in the highest enantioselectivities. ^{n}BuLi consistently gives more modest results. The presence of lithium salts in alkyllithium reagents was thought to inhibit the reaction by their coordination to the ligand. However, when freshly prepared vinyllithium was used, again only modest enanantiomeric excesses were obtained in most cases. That free salts were not a problem seems to be confirmed by the absence of improvement in enantioselectivity when using 4 equiv of external ligand. Of the four ligands studied, the best results have consistently been with the diethers **5** and **6**. There is a rapid fall-off in enantioslectivity when the number of equivalents of external ligand used is reduced. A tentative interpretation of the results is that the reacting nucleophile is oligomeric rather than monomeric, with ligands acting as bridges rather than chelates. We are currently attempting to isolate and characterize the reaction intermediate. This will show ligand and nucleophile arrangement and could result in a better ligand design for a better complex match.

Scheme 2



R=Ph: (+)-**8a** (64 %, 93 % ee)
vinyl: (+)-**8b** (77 %, 75 % ee)
Me: (+)-**8c** (62 %, 91 % ee)

First results of the use of the application of this methodology to an imine complex are shown in Scheme 2.

In the examples described with the phenyloxazoline complex, the methodology presented here is complementary to that developed with chiral oxazolines. The reactions with the imine complex **7** are unique in that there are as yet no chiral imines which give both high 1,4-regio- and diastereocontrol in arene addition reactions.[11]

In summary, we have extended the previously reported stereo- and regioselective reactions into an asymmetric version by the use of external chiral ligands. This circumvents the problem of additional steps of incorporating (and removing) a chiral auxiliary in the arene and is, therefore, potentially a more general method.[12] Combine this with the potential for catalysis or at least for further optimization of the significant enantioselectivities obtained so far, and an attractive method for asymmetric additions across an arene double bond presents itself.

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Supporting Information Available: Experimental details and characterization data for ligand (1*S*,2*S*)-(+)-**5**. Representative procedures for sequential additions to complexes **1** and **7**. Listings of ^{1}H- and ^{13}C-NMR , IR, MS, and chiral HPLC (or GC) data for cyclohexadienecarbaldehydes **8a**−**c** (3 pages).

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(8) (−)-Sparteine (**3**): Fluka. For a recent example of the catalytic use of sparteine in asymmetric additions to aldehyde imines see ref 1c. For recent references of the use of sparteine in enantioselective deprotonations see: (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (b) Guarnieri, W.; Grehl, M.; Hoppe, D. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 1734.

(9) Ether (1*R*,2*R*)-**4**, (1*S*,2*S*)-**5**, and (1*S*,2*S*)-**6** were obtained in high yield from the diols (1*R*,2*R*)-**9**, (1*S*,2*S*)-**10**, and (1*S*,2*S*)-**11**, respectively (all >99% ee), by reaction with NaH and dimethyl sulfate. (a) Diol (1*R*,2*R*)-**9** is available commercially (Fluka). (b) Diol (1*S*,2*S*)-**10** was obtained by a literature procedure: Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 49. (c) Diol (1*S*,2*S*)-**11** was obtained by a literature procedure: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (d) For previous application of **4** and **6** as chiral ligands for organolithium reagent additions to naphthalenes see ref 2.

(10) For enantioselective *ortho*-deprotonations of prochiral arene Cr(CO)$_3$ complexes by alkyl Li reagents/chiral ligands or by chiral amide bases see: (a) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt. A. P. *J. Org. Chem.* **1994**, *59*, 1961. b) Kündig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497. (c) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron Asymm.* **1994**, *5*, 1427. (d) Schmalz, H. G.; Schellhaas, K. *Tetrahedron Lett.* **1995**, *36*, 5515.

(11) SAMP-hydrazones can be used effectively in diastereoselective nucleophilic additions to (arene)Cr(CO)$_3$ complexes, but compared to imines, hydrazones are far more resistant to nonoxidative hydrolyis. Kündig, E. P.; Liu, R.; Ripa, A. *Helv. Chim. Acta* **1992**, *75*, 2675.

(12) Enantioselectivities need to be high though. A significant convenience of diastereoselective reactions lies in the easy product separation of diastereomeric products.