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Mini-Account

Contra-intuitive stereocontrol: *endo*-selective nucleophilic additions on an arene–tricarbonylchromium template

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Abstract

In arene–tricarbonylchromium complexes, *exo*-selectivity is the normal. This account, on the other hand, summarizes our results of *endo*-selective nucleophilic additions with very high stereocontrol at relatively remote sites, which enhances the potential of these complexes as synthons for target synthesis. © 2001 Published by Elsevier Science B.V.

Keywords: Arene–tricarbonyl complexes; *Endo*-selectivity

The planar chirality associated with appropriately substituted arene–tricarbonylchromium complexes has been extensively investigated to provide useful synthons for a variety of targets ranging from biologically relevant molecules to chiral chelating ligands for metals in asymmetric catalysis [1]. Available methodology to resolve arene–chromium complexes [2] permitted synthesis of numerous such target molecules in enantiopure form. The relative facility of reagent approach to the stereoface from a direction opposite to the tricarbonylchromium group — *exo*-selectivity — has been used conveniently to create new stereogenic centers in these molecules with high stereocontrol — either at the benzyl or homobenzyl sites, or on the aryl ring itself, which gets transformed to cyclohexadiene derivatives [3]. A stage is therefore reached when one can conceptually integrate such methodologies into tailored approaches to multi-functionalized cyclic or acyclic structures (Scheme 1).

The scope of this strategy would extend manifold if stereocontrol could be achieved also at sites away from the immediate vicinity of complexed arene ring. In this context, the arylidene derivative resulting from condensation of a tetralone complex with an aromatic aldehyde was perceived to be an ideal substrate [4]: its rigid, planar framework of π-system extending well beyond the periphery of arene ring offers a reactive, electrophilic center residing three carbons away from the complexed arene ring, and three contiguous, potential stereogenic centers waiting to be created allow one to test the efficiency of stereocontrol in one-step or sequential functionalizations (Chart 1). The chemical shift value of the =C(H)Ar proton at 7.8 ppm (s) was used to ascertain the alkene geometry [5], which is a crucial structural element based on which steric course of reactions are defined. The present article recounts our results of addition reactions on this class of substrates, which revealed contra-intuitive reversal of normal stereochemical bias — a preference for *endo* selectivity — in more than one instance.

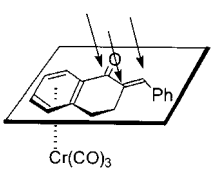

Chart 1.

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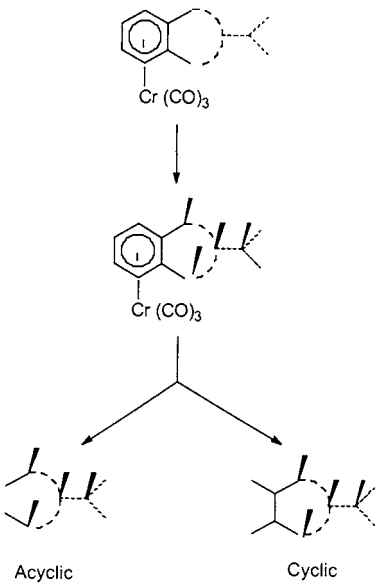
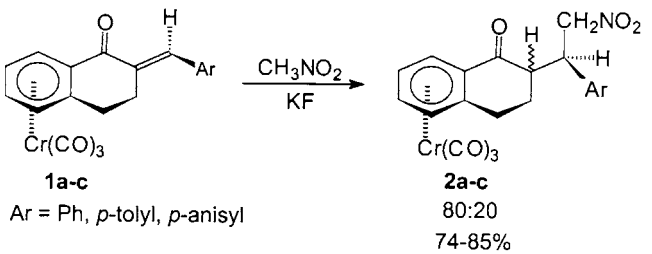
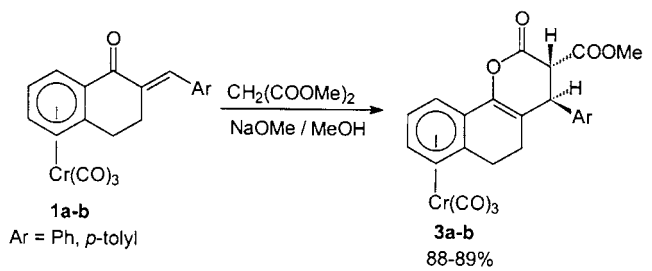


Scheme 1.



Scheme 2.



Scheme 3.

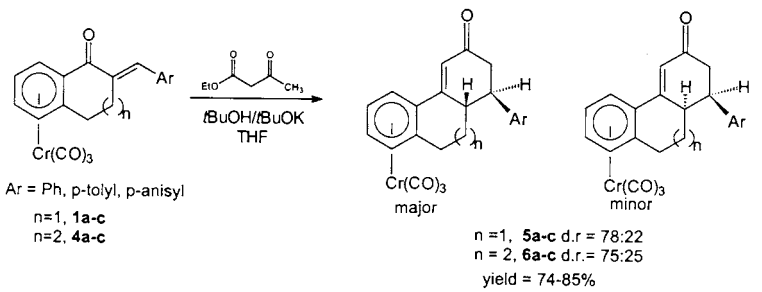
The first set of experiments was concerned with nucleophilic additions to the enones anchored on arene–tricarbonylchromium template. Nitromethane added in a conjugate manner exclusively from the *exo*-face despite its small size even at room temperature (Scheme 2). The addition at C-3 was entirely stereoselective but diastereoisomers resulted from equilibration due to presence of acidic protons adjacent to the carbonyl function [6]. The rate of reaction was significantly greater than addition to uncomplexed substrate, as would be normally expected.

The stereoselectivity of conjugate addition was equally high (only the isomers resulting from *exo*-selective addition at C-3 were isolated in high yield) when other simple nucleophiles such as dimethyl malonate (Scheme 3) and ethyl acetoacetate (Scheme 4) were used at ambient temperature [7]. Benzosuberone analogs reacted with comparable facility and outcome.

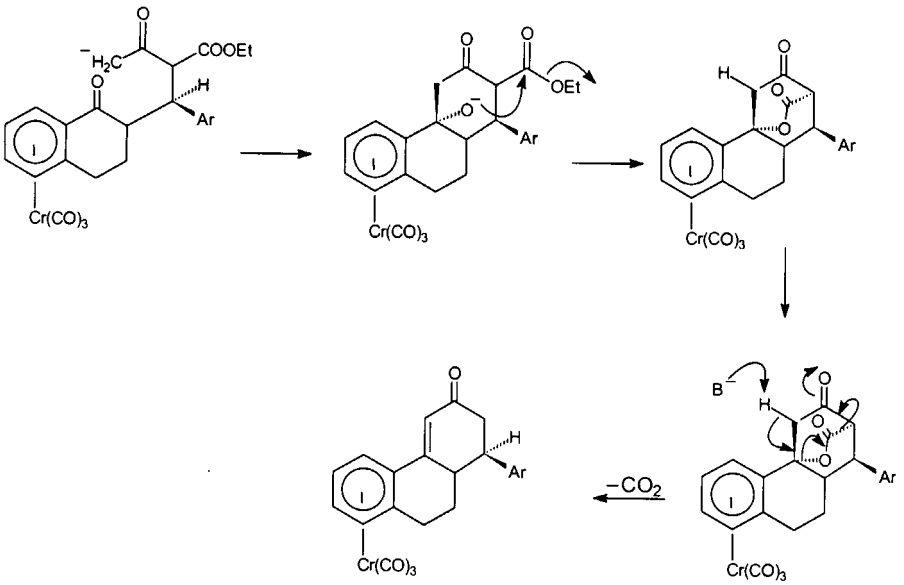
While the stereochemistry of products derived from dimethyl malonate has been tentatively assigned, structures of annulated derivatives obtained from addition of ethyl acetoacetate were confirmed on the basis of crystal structure determination of major isomers and equilibration studies (the isomers result from enolization of vinylogously active, acidic protons present in these molecules). The annulation depicted in Scheme 5 also presents a rare in situ decarboxylation not commonly encountered at ambient temperature. Neither the addition of ethyl acetoacetate to the uncomplexed enone is rapid, nor the product profile is as clean as observed for the complexed substrate. The rationale put forward for the decarbethoxylation is displayed in Scheme 5. According to this suggestion, both the formation of *endo*-cyclic lactone and subsequent extrusion of carbon dioxide must be fast steps, since no intermediate was observed (TLC) during the course of this reaction.

Enolates derived from enol silanes of acetone or acetophenone by fluoride or potassium hydride in DMF, add with high *exo*-selectivity to C-3, highlighting the generality of such reactions [8].

To override the problem of base-catalyzed epimerization, one has to select reactions where a rapid electrophilic quench of the intermediate



Scheme 4.



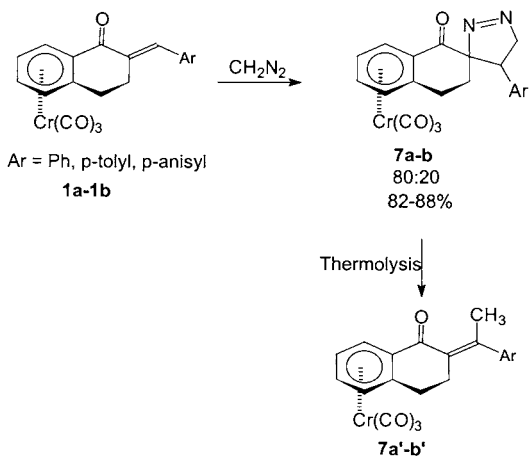
Scheme 5.

enolate — preferably an intramolecular reaction — would produce a stable C–C bond instead of a labile C–H bond prone to enolization. Although the organized transition state of a concerted 3 + 2 cycloaddition with diazomethane appeared to be an attractive feature for high stereodifferentiation, preliminary experiments provided a disappointing selectivity of 80:20 [4]. The stereoisomers were, nevertheless, separately isolated, but on thermolysis they afforded the same β-methyl enone product instead of a cyclopropane (Scheme 6).

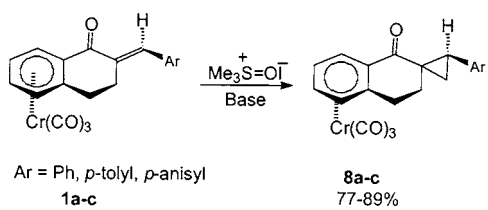
However, cyclopropanation by sulfoxonium methylide — either generated in situ from sulfoxonium salt under phase-transfer condition (50% aq. NaOH and dichloromethane, ca. Bu_4NBr at 45°C) or preformed in THF at room temperature — afforded a high yield of diastereomerically pure product [9]. Contrary to expectation based on precedents described above, the crystal structure revealed the product to be an *endo*-cyclopropane (Scheme 7). This product could form only by an *endo*-addition of the nucleophile followed by a fast ring-closure — faster than a C–C bond rotation — so that both new bonds are formed from the *endo*-face.

We could think of two possible explanations. Nucleophilic attack of sulfoxonium ylide to enone is known to be reversible. The *endo*-product could then result from a faster ring-closing step that is irreversible and shift the initial equilibrium in favor of *endo*-selective initial addition. Alternatively, the ylide could have first coordinated to $Cr(CO)_3$ group to be delivered from the *endo*-face intramolecularly. Considering the reaction temperature and yet the high selectivity, we prefer the metal-mediated delivery as the more acceptable mechanism, but this aspect awaits further experimental confirmation. However, the theme of contra-intuitive, *endo*-selective transformations continued to recur in the studies that followed.

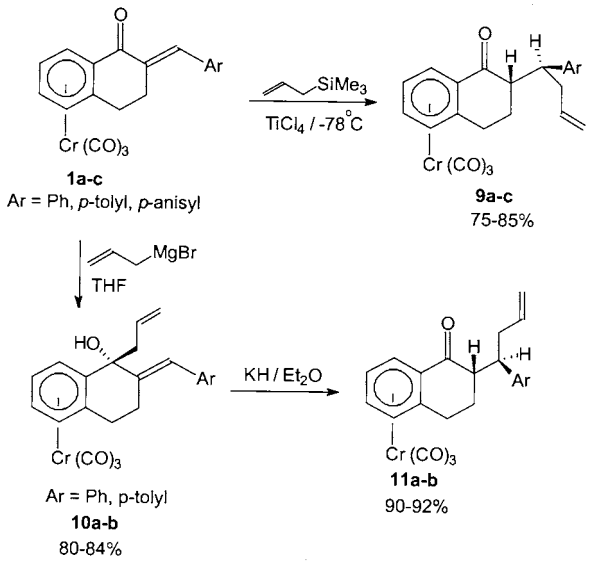
An allyl group is a versatile appendage that can be transformed into a wide variety of functional groups at an appropriate stage of a synthetic plan. A Hosomi–Sakurai reaction allows the addition of allyl groups to



Scheme 6.



Scheme 7.



Scheme 8.

enones in a conjugate manner [10]. But it is an electrophilic process promoted by strong Lewis acids like $TiCl_4$ — unlike the base-catalyzed nucleophilic reactions described so far. It is carried out at a low temperature (typically at $-78°C$) in an aprotic solvent, and quenched also at a low temperature to expose the product briefly to an acidic medium. We perceived that such a condition might not induce rapid epimerization at C-2. The stereochemistry of the product was sought to be established by a straightforward chemical correlation. Addition of allyl magnesium bromide would provide the 1,2-addition product, which should undergo an anionic oxy-Cope rearrangement stereoselectively (along the *exo*-face of the molecule) to yield the same product as obtained from the Hosomi–Sakurai allylation.

The Hosomi–Sakurai reaction on substrates **1a–c** did produce a diastereomerically pure product in high yield. The Grignard addition to the same substrate followed by anionic oxy-Cope rearrangement produced a distereomerically pure product as well (Scheme 8). But the proton NMR spectra revealed that while the two products were indeed isomeric, they were not identical. Base-induced equilibration led to the production of two additional isomers. Isolation of all possible isomers in this manner indicated that the original Hosomi–Sakurai product and the one obtained from the two-step sequence were epimeric at C-3. Crystal structure determination of these two complexes confirmed that the Hosomi–Sakurai reaction actually produced an *endo*-allylated product [11], and the proton quench occurred at C-2 from the *exo*-face.

The apparently anomalous stereochemical outcome of the Hosomi–Sakurai reaction can be explained if it is recognized that the carbonyl group of the substrate is flanked by two hydrogens — approximately coplanar — and a Lewis acid coordination to carbonyl oxygen from the direction of either lone pair is sterically unfavorable. Since the tricarbonylchromium unit blocks the *endo*-face of the carbonyl function, the titanium cation must coordinate to the carbonyl oxygen from the *exo*-face of the substrate (Chart 2). The $TiCl_4$ is likely to exist as aggregates in a non-coordinating solvent like dichloromethane and it would crowd the *exo*-face as well. Hence the allylsilane would be forced to react from the less favored, but now more accessible, *endo*-face. This explanation relies heavily on the ability of strong Lewis acidic metals to coordinate with carbonyl functions in an out-of-plane manner [12].

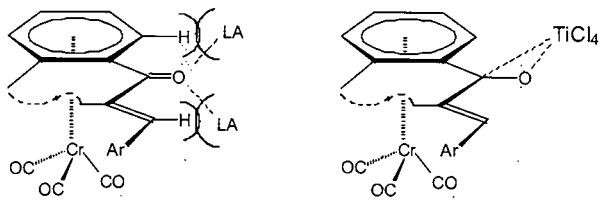


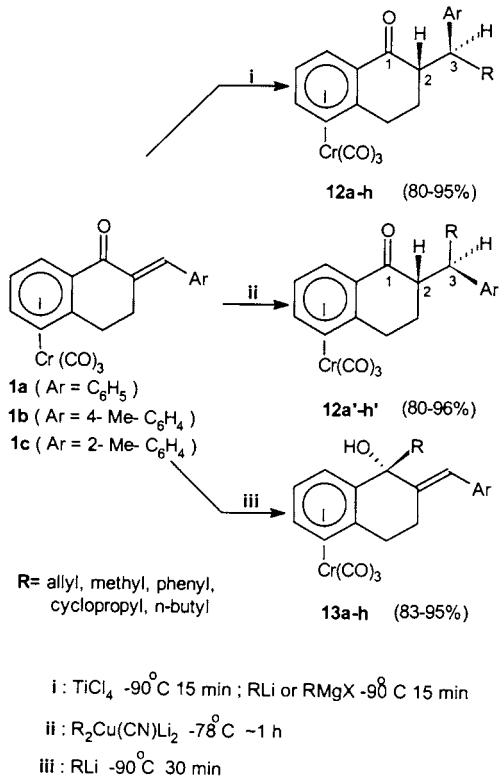
Chart 2.

The other possible explanation for observed *endo*-selectivity of allylation would presuppose complexation of $TiCl_4$ with the oxygens of the carbonyl ligand, thereby directing the allylsilane from the *endo*-face. A control reaction was performed under the same condition with acetophenone enolsilane in place of allyltrimethylsilane [5]. The diastereomerically pure product obtained from this reaction was identical with the one obtained from a hydride-mediated conjugate addition [13], which should normally occur from the *exo*-face of the enone. It is reasonable to expect that the oxygen of the enolsilane would coordinate with highly Lewis acidic titanium cation as well prior to reaction and would have access to the *exo*-face only if $TiCl_4$ binds to the ketone carbonyl of the substrate from the same face. This experimental result thus provides an argument against the possibility of $TiCl_4$ preferentially binding with carbonyl ligands rather than the carbonyl function of the substrate.

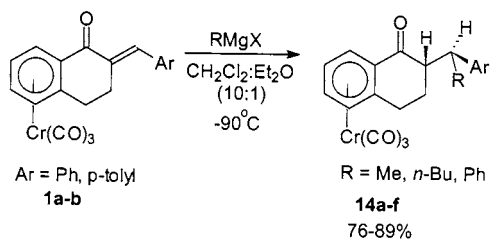
The out-of-plane coordination of $TiCl_4$ to an arylidene–tetralone complex, leading to a reversal of stereochemical preference, inspired an attempt to examine whether addition of strong nucleophilic reagents to these substrates pretreated with $TiCl_4$ would reproduce a similar *endo*-selective trend. In absence of $TiCl_4$, simple alkyl and aryllithiums added to the enone complexes to provide predominantly 1,2-adducts with complete *exo*-selectivity. For the reaction with substrates pretreated with 2–5 equivalents of $TiCl_4$, dichloromethane was retained as the major component of the solvent to maximize Lewis acid–carbonyl complexation. Although we were initially apprehensive about the compatibility of dichloromethane with reactive RMgX reagant, we later found that such a combi-

nation has been used earlier [14]. The organolithium reagents were prepared in ether or THF and added (−90°C) to the substrate such that the ratio of dichloromethane and ether solvent is approximately 10:1. Under these conditions, the reaction yielded only 1,4-addition products with *endo*-selectivity (Scheme 9).

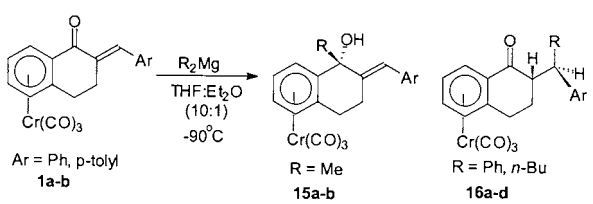
If BuLi was first treated with $TiCl_4$ and the substrate added subsequently, the starting material was recovered unchanged. Indeed, the facile β-hydride elimination pathway for decomposition of such organotitanium species is well known. The successful reaction with BuLi and cyclopropyllithium in presence of $TiCl_4$ in these reactions indicated that organotitanium reagents were not involved in these reactions, nucleophilic addition took place much faster than transmetallation. The corresponding *exo*-adducts were obtained by addition of cuprates in absence of Lewis acid. Together, these two routes constitute a stereodivergent protocol of alkylation of these complexes [15].



Scheme 9.



Scheme 10.



Scheme 11.

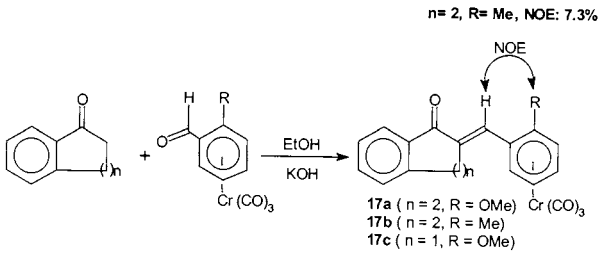
We have subsequently discovered that $TiCl_4$ is not a unique Lewis acid that permits such reversal of stereoface preference on arene–chromium template. Grignard reagents have been found to proceed in *endo*-selective manner to provide 1,4-adducts, though allyl-Grignard reagents remained an exception (Scheme 10).

Conceivably, the magnesium bromide generated in the reaction as a result of Schlenck equilibrium [16] acts as a Lewis acid in this reaction. At least two equivalents of reagent were necessary to drive the reaction to completion. Yet the products were obtained consistently in high yield and diastereomeric purity. In order to establish the role of magnesium halide further, additions were performed with dialkyl- or diarylmagnesium reagents in presence and absence of magnesium salts (Scheme 11).

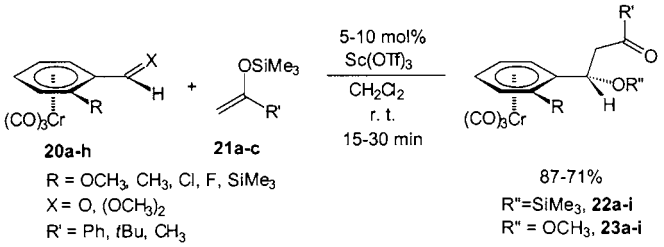
The dialkylmagnesiums afforded *endo*-1,4-adducts when substrates were pretreated with magnesium halide, independent of the size of the alkyl group. Similarly, organolithium reagents afforded *endo*-1,4-adducts in presence of magnesium halide. These experiments imply that magnesium halide indeed plays a decisive role in determining stereochemical and regiochemical course of nucleophilic additions to conformationally rigid enone substrates [17].

The spatial relationship between the reacting terminus and the tricarbonylchromium moiety seems crucial too. Because of its immediate proximity, *endo*-selective nucleophilic addition at a benzylic site is not feasible [18]. However, it is possible to introduce an allyl group from the *endo*-face of the molecule to a benzylic site by a two-step protocol: an *endo*-selective allylation at a remote site, followed by a concerted rearrangement to transfer the allyl group to a benzylic position of chromium complexed arene ring [19]. The preparation of substrates is depicted on Scheme 12. An NOE difference spectrum established the orientation of the *ortho*-substituted complexed arene ring.

This complex does not undergo a Hosomi–Sakurai reaction because the prospective reaction site is too close to the complexed arene ring to permit *endo*-addition when the *exo*-face is protected by $TiCl_4$ aggregate. On the other hand, allyllithium added to the carbonyl function from the *endo*-face selectively in presence of the Lewis acid. An anionic oxy-Cope rearrangement



Scheme 12.



Scheme 14.

subsequently introduced the allyl group to the benzylic position from the *endo*-face. The *exo*-isomer could be readily obtained by eliminating the Lewis acid during allyllithium addition and carrying out the rearrangement as before. The product stereochemistry for both isomers was confirmed by crystal structure determination (Scheme 13).

In spite of our best efforts, with conformationally labile, *ortho*-substituted acyclic enone substrates, a definite correlation of stereochemical preference as a function of Lewis acid employed, so far remained elusive. However, it was encouraging to note that *ortho*-substituted benzaldehyde complexes retain clear preference for *syn–anti* orientation between the substituent and the planar CO group at room temperature so that only one diastereotopic face is accessible for nucleophilic addition. Gratifyingly, scandium or rare earth triflates catalyzed [20] highly diastereoselective aldol reactions with aldehyde as well as acetal complexes (Scheme 14). The relationship of diastereotopic carbonyl function in aldehyde and benzylic cation generated from the corresponding acetal is displayed in Chart 3, and it was established by comparing CD spectra of products obtained from optically active substrates [21].

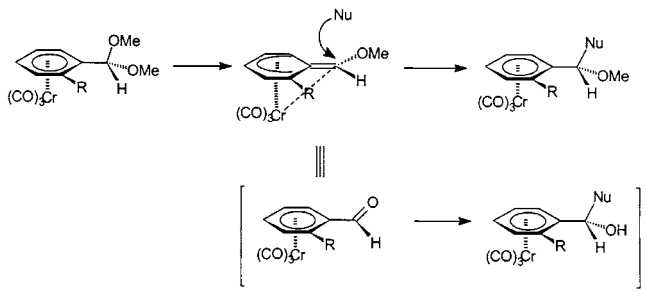
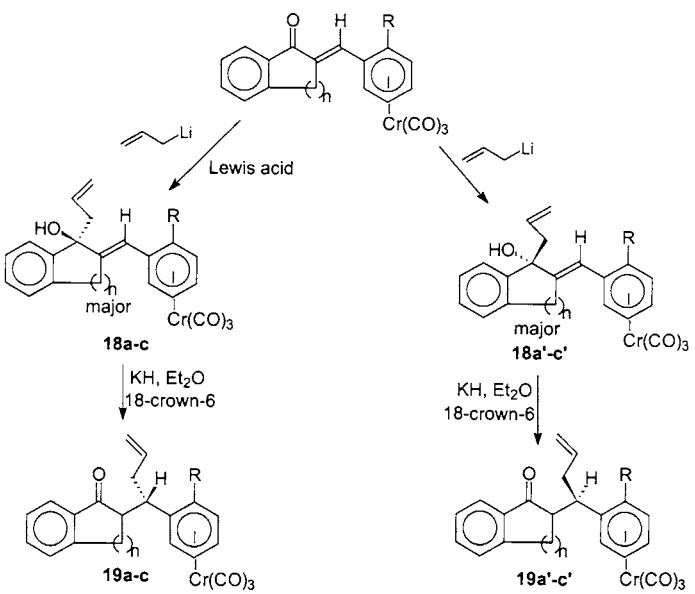


Chart 3.

The study is currently being extended to related acyclic imine derivatives — preliminary experiments provided diastereomerically pure amino carbonyl compounds and β-lactams by a simple procedure [22]. The merit of these reactions obviously lies in the ease and convenience of operation at ambient temperature, coupled with a wide functional group tolerance.

In summary, we have shown that it is possible to attain highly diastereoselective nucleophilic addition to conformationally rigid arene chromiumtricarbonyl



Scheme 13.

complexes even at sites three carbons away from the complexed arene ring. We also discovered that the presence of a Lewis acid can predictably and efficiently reverse the normal *exo*-selectivity trend in these complexes to afford *endo*-addition products. We do not know if the tendency of the Lewis acid to coordinate in an out-of-plane manner is intrinsic to a reaction or induced by steric factors detrimental to in-plane coordination motif. This question is relevant to transition state structures of a wide variety of chiral Lewis acid-catalyzed reactions. Also, in a broader perspective, arene–tricarbonylchromium complexes represent only one variety of several synthetically useful π-complexes with stereodifferentiated π-faces (planar chirality). The concept of stereoreversal in presence of Lewis acid in suitably functionalized complexes is, in principle, adaptable to any such metal-template. In addition, conformationally biased, rigid organic structures also should be interesting substrates to study this phenomenon. Further exploration in this direction is in progress.

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References

[1] For recent examples of application in synthesis, see: (a) K. Kamikawa, T. Watanabe, A. Daimon, M. Uemura, Tetrahedron 56 (2000) 2325. (b) G.B. Jones, M. Guzel, J. Mathews, Tetrahedron Lett. 41 (2000) 1123. (c) H. Ratni, B. Crousse, E.P. Kundig, Synlett 5 (1999) 626. (d) C. Baldoli, D. Buttero, P. Paola, P. Dario, Tetrahedron 55 (1999) 14089. (e) B. Schnell, G. Bernardinelli, E.P. Kundig, Synlett 3 (1999) 348. (f) H. Koide, M. Uemura, Chem. Commun (1998) 2483. (g) A. Majdalani, H.-G. Schmalz, Synlett 11 (1997) 1303. (h) A. Fretzen, A. Ripa, R. Liu, G. Bernardinelli, E.P. Kundig, Chem. Eur. J. 4 (1998) 251. (i) K. Schellhaas, H.-G. Schmalz, J.W. Bats, Chem. Eur. J. 4 (1998) 57. (j) K. Schildknegt, J. Aube, Chemtracts 10 (1997) 1. (k) G.B. Jones, R.S. Huber, B.J. Chapman, Tetrahedron Asymmetry 8 (1997) 1797. For methodologies, see: (l) S.E. Gibson, P. Ham, G.R. Jefferson, Chem. Commun. (1998) 123. (m) A. Ariffin, A.J. Blake, R.A. Ewin, N.S. Simpkins, Tetrahedron Asymmetry 9 (1998) 2563. (n) S. Malfait, L. Pelinski, J. Brocard, Tetrahedron Asymmetry 9 (1998) 2595. For recent reviews, see: (o) C. Bolm, K. Muniz, Chem. Soc. Rev. 28 (1999) 51. (p) S. Perrio, in: S.E. Gibson (ed.), Transition Metal Organic Synthesis, Oxford University Press, Oxford, UK, 1997, p. 167.

[2] M. Uemura, Tricarbonyl (η^6 arene) chromium complexes in organic synthesis, in: L.S. Liebeskind (Ed.), Advances In Metal–Organic Chemistry, vol. 2, JAI, Greenwich, CT, 1991, p. 231 and Refs. [84–110] cited therein.

[3] (a) M.F. Semmelhack, Transition metal arene complexes: nucleophilic additions, in: E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Comprehensive Organometallic Chemistry, Part II, vol. 12, Pergamon, Oxford, 1995, p. 979. (b) S.G. Davies, T.D. McCarthy, Transition metal arene complexes: side chain activation and control of stereochemistryin: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 12, Pergamon, Oxford, 1991, p. 1039. (c) M.F. Semmelhack, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, vol. 4, Pergamon, Oxford, 1991, p. 517. (d) A.R. Pape, K.P. Kalliappan, E.P. Kundig, Chem. Rev. 100 (2000) 2940.

[4] S. Ganesh, Studies in Stereoselective Transformations on Arene Chromium Template, Ph.D. Dissertation submitted to the University of Poona, 1993.

[5] The corresponding chemical shift value of the other geometric isomer is 6.4 ppm. We thank a referee of the Journal of Organic Chemistry for bringing our attention to this. For details, see: S. Sur, Stereoselective Transformations on Arene Tricarbonylchromium Complexes, Ph.D. Dissertation submitted to the University of Poona, 1997.

[6] S. Ganesh, A. Sarkar, Tetrahedron Lett. 32 (1991) 1085.

[7] S. Sur, S. Ganesh, V.G. Puranik, A. Sarkar, J. Chem. Soc. Perkin Trans. (1998) 977.

[8] S. Sur, unpublished results.

[9] S. Ganesh, K.M. Sathe, M. Nandi, P. Chakrabarti, A. Sarkar, J. Chem. Soc. Chem. Commun. (1993) 224.

[10] (a) A. Hosomi, Acc. Chem. Res. 21 (1988) 200. (b) J.S Panek, in: B.M Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 1, Pergamon, Oxford, 1991, p. 579. (c) Y. Yamamoto, N. Sasaki, in: I. Bernal (Ed.), Stereochemistry of Organometallic and Inorganic Compounds, vol. 3, Elsevier, Amsterdam, 1989, p. 363. (d) I. Fleming, in: D.H. Barton, W.D. Ollis (Eds.), Comprehensive Organic Chemistry, vol. 3, Pergamon, Oxford, 1979. (e) I. Fleming, J. Dunogues, R. Smithers, Organic Reactions, Wiley, Chichester, 1989, pp. 37 and 57. (f) H. Sakurai, Pure Appl. Chem. 54 (1982) 1. (g) E. Colvin, Silicon in Organic Synthesis, Butterworths, London, 1981. (h) A. Hosomi, H. Sakurai, J. Am. Chem. Soc. 99 (1977) 1673.

[11] S. Sur, S. Ganesh, D. Pal, V.G. Puranik, P. Chakrabarti, A. Sarkar, J. Org. Chem. 61 (1996) 8362.

[12] (a) For a review on Lewis acid–carbonyl complexation, see: S. Shambayati, S.L. Shrieber, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic synthesis, vol. 1, Pergamon, Oxford, 1991, p. 283. (b) Detailed spectroscopic studies on Lewis acid–carbonyl have been carried out by Denmark in order to probe stereoselectivity in Lewis acid promoted reactions, see: S.E. Denmark, N.G. Almstead, Tetrahedron 48 (1992) 5565 and Refs. [12,13] cited therein. A study with extensive references on the importance of out-of-plane complexes in titanium in promoting organic reaction appeared in: D.K. Singh, J.B. Springer, P.A. Goodson, R.C. Corcoran, J. Org. Chem. 61 (1996) 1436. Refs. [21a–I] in this paper provides a collection of relevant dihedral angle data from CSD.

[13] For use of alkali metal hydrides as nucleophiles in desilylation, see: (a) S.K. Mandal, A. Sarkar, J. Org. Chem. 63 (1998) 5672. (b) S.K. Mandal, A. Sarkar, J. Org. Chem. 63 (1998) 1901. (c) V.M. Swamy, A. Sarkar, Tetrahedron Lett. 39 (1998) 1261.

[14] A. Bongini, G. Cardillo, A. Mingardi, C. Tomasini, Tetrahedron Asymmetry 7 (1996) 1457.

[15] S.K. Mandal, A. Sarkar, J. Org. Chem. 64 (1999) 2454.

[16] K.C. Cannon, G.R. Krow, The composition of Grignard reagents in solution. The Schlenk equilibrium, in: G.S. Silverman, P.E. Rakita (Eds.), Handbook of Grignard Reagents, Marcel Dekker, New York, 1996, p. 271.

[17] V.M. Swamy, S.K. Mandal, A. Sarkar, Tetrahedron Lett. 40 (1999) 6061.
[18] G. Jaouen, A. Meyer, J. Am. Chem. Soc. 97 (1975) 4667.
[19] S.K. Mandal, A. Sarkar, in preparation.
[20] (a) S. Kobayashi, I. Hachiya, T. Takahori, Synthesis (1993) 37. (b) S. Kobayashi, I. Hachiya, Tetrahedron Lett. 33 (1992) 625. (c) S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, Synlett (1993) 472. (d) S. Kobayashi, I. Hachiya, J. Org. Chem., 9 (1994) 3590.
[21] V.M. Swamy, M. Bhadbhade, V.G. Puranik, A. Sarkar, Tetrahedron Lett. 41 (2000) 6137.
[22] B.C. Maity, A. Sarkar, in preparation.