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Toolbox Approach to the Search for Effective Ligands for Catalytic Asymmetric Cr-Mediated Coupling Reactions

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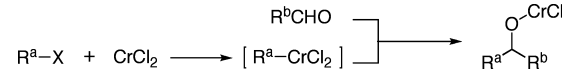
Abstract: Chromium catalysts derived from chiral sulfonamides represented by **A** effect the couplings of aldehydes with vinyl, allyl, or alkyl halides. With three distinct sites for structural modification, **A** affords access to a structurally diverse pool of chiral sulfonamides. The Cr catalysts derived from these sulfonamides exhibit a broad range of catalyst−substrate matching profiles. A strategy is presented to search for a satisfactory chiral sulfonamide for a given substrate. In order to demonstrate the *generality and effectiveness* of this approach, five diverse C−C bond-forming cases have been selected from the halichondrin synthesis. For each of the cases, two ligands have been deliberately searched for, to induce the formation of (*R*)- and (*S*)-alcohols, respectively, at the arbitrarily chosen efficiency level of "≥80% yield with ≥20:1 stereoselectivity in the presence of ≤20 mol % of a Cr catalyst". For 9 out of the 10 cases studied, a satisfactory catalyst has been found within this pool of sulfonamides. Even for the remaining case, a Cr catalyst inducing stereoselectivity up to 8:1 has been identified.

1. Introduction

Cr(II)-mediated addition of allyl halides/triflates to aldehydes was reported by Hiyama, Nozaki, and co-workers in 1977.[1] In this reaction, the active nucleophiles $RCrX_3$ were generated *in situ* via oxidative addition of Cr(II) to allyl halides/triflates (Scheme 1). Since then, new methods have been developed to form the active nucleophiles $RCrX_3$ from a wide range of halides and triflates.[2] Depending on the activation methods, Cr-mediated couplings are now divided into three subgroups: (1) Ni/Cr-mediated alkenylation, alkynylation, and arylation;[3] (2) Co- or Fe/Cr-mediated alkylation, 2-haloallylation, and propargylation;[4] and (3) Cr-mediated allylation and propargylation.

Overall, the Cr-mediated C−C bond-forming reaction is viewed as a Grignard-type carbonyl addition of halides. However, it is noteworthy that this reaction displays a remarkable selectivity toward aldehydes over other carbonyl compounds. Activation of halides in the presence of aldehydes provides us with not only an experimental convenience but also an opportunity to realize chemical transformations in an unconventional manner, cf., cyclization.[5] Undoubtedly, the most valuable feature of this reaction is its exceptional compatibility with a wide range of functional groups. This unique potential is appreciated most when applied to polyfunctional molecules. There are numerous examples in which this reaction has been successfully used at a late stage in a multistep synthesis.[6]

Scheme 1. Cr(III)-Mediated Couplings



For its application to a practical synthesis, it is desirable to develop a catalytic process for the Cr-mediated coupling reaction. In 1996, Fürstner and Shi reported a catalytic version of this reaction, in which TMS-Cl and Mn(0) are used as a dissociating agent of chromium alkoxides and a reducing agent of chromium, respectively (step 4 and step 1 in Scheme 2).[7]

Mn(0) is the most effective agent to reduce Cr(III) and regenerate Cr(II).[8] TMS-Cl is an effective dissociating agent,

(1) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.

(2) For reviews on Cr-mediated carbon−carbon bond-forming reactions, see: (a) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. *1*, p 173. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (c) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (d) Takai, K.; Nozaki, H. *Proc. Jpn. Acad. Ser. B* **2000**, *76*, 123. (e) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.

(3) (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

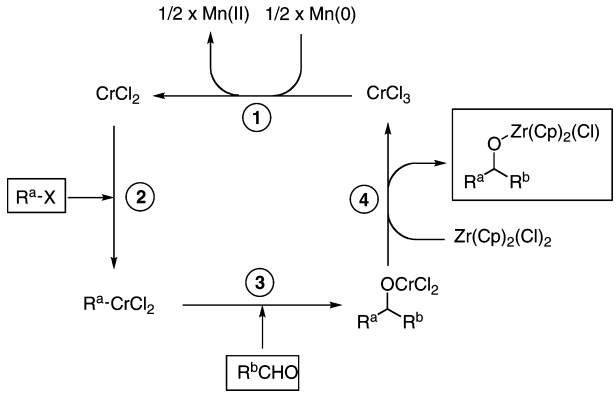
(4) (a) Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. *J. Org. Chem.* **1989**, *54*, 4732. (b) Choi, H.-w.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. (c) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(5) For examples, see: (a) Schreiber, S. S.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. (b) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. (c) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382.

(6) For examples, see: (a) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7530. (b) Aicher, T. D. K.; Buszek, R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (c) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1157.

(7) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (c) Fürstner, A.; Wuchrer, M. *Chem.−Eur. J.* **2006**, *12*, 76.

Scheme 2. Catalytic Cycle of Cr-Mediated Coupling Reactions[a]



[a] For the activation of halides (step 2), see panels A and B in Scheme 4.

but we found that $Zr(Cp)_2Cl_2$ is a more effective dissociating agent.[9h] The difference between TMS-Cl and $Zr(Cp)_2Cl_2$ is twofold. First, the catalytic Cr-mediated coupling in the presence of TMS-Cl does not proceed to completion for enolizable aldehydes, because of silyl enol ether formation; upon aqueous workup, typically 10−20% of the aldehyde is recovered, which is recyclable for many cases. However, for the enolizable aldehydes bearing a chiral center at the carbon adjacent to the aldehyde, the recovered starting material may not maintain its stereochemical homogeneity. To the contrary, in the presence of $Zr(Cp)_2Cl_2$, the coupling proceeds smoothly to completion without presenting this problem.[9h] Second, the coupling rate with $Zr(Cp)_2Cl_2$ is significantly faster than that with TMS-Cl.

Overall, the $Zr(Cp)_2Cl_2$/Mn system is effective for regenerating the catalyst employed for all the subgroups of Cr-mediated couplings. Coupled with this system, it is now possible to achieve the Cr-mediated coupling reactions in the presence of 1 mol % of the Cr catalyst prepared from $CrCl_3 \cdot 3THF$ and 3,3′-dimethyl-2,2′-dipyridyl or 4,4′-di-*tert*-butyl-2,2′-dipyridyl.[9j]

Several ligands have been reported to induce asymmetric Cr-mediated couplings under stoichiometric and/or catalytic conditions.[10] We have reported that the catalyst prepared from $CrCl_2$ and (*S*)-sulfonamide **1** (Figure 1) is effective to achieve asymmetric couplings under stoichiometric and catalytic conditions.[9d−g,i,l] On the basis of the X-ray structure of Cr(III)(**1**$^-$)$(Cl)_2$, Cr(III)(**1**$^-$)(Me)(Cl), and Cr(II)(4-*t*-Bu-py)$_3(Cl)_2$ complexes (Figure 1), we proposed that the sulfonamide-based asymmetric coupling reaction proceeds through the intermediates depicted in Scheme 3. In this proposal, the Cr catalyst maintains the octahedral structure throughout the catalytic cycle, and all the events take place at only two ligation sites of the octahedral catalyst.[9d]

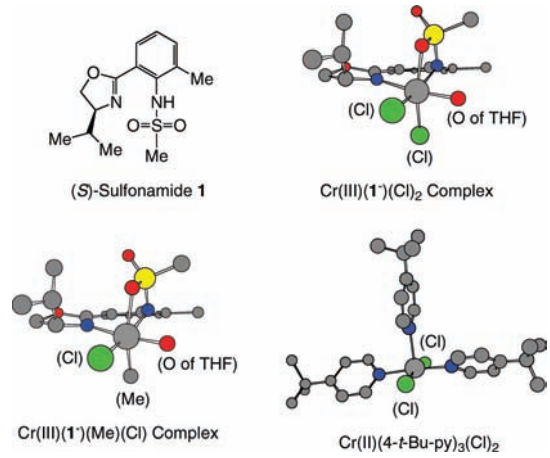
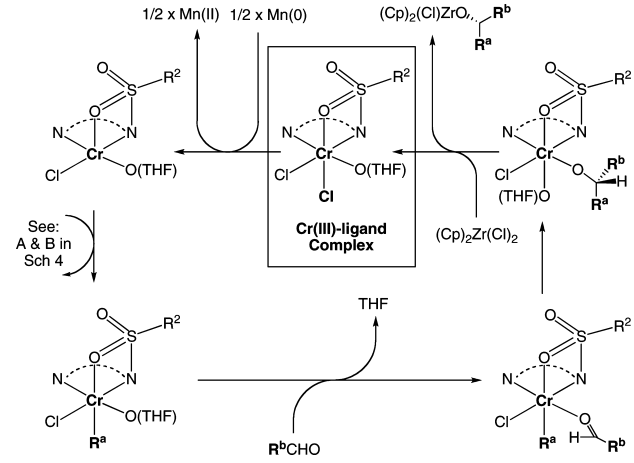


Figure 1. Structure of the first generation of (*S*)-sulfonamide **1** and three X-ray structures of Cr complexes.

Scheme 3. Proposed Structures of the Cr(III) Species Involved in the Catalytic Coupling Reaction



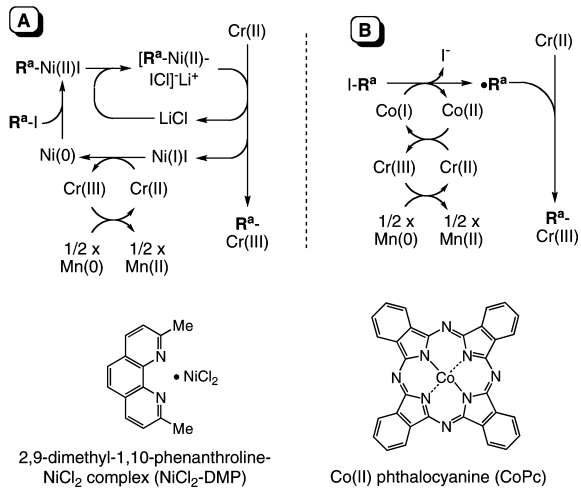
In order to achieve asymmetric Ni/Cr-mediated coupling under the catalytic conditions, the Ni catalyst needs to meet two criteria. First, the Ni salt must have an efficient catalytic cycle (panel A in Scheme 4). Second, the Ni catalyst should not interfere with the asymmetric process induced by the chiral Cr-sulfonamide ligand. Among many Ni(II) complexes tested, the 2,9-dimethylphenanthroline/$NiCl_2$ complex ($NiCl_2 \cdot$DMP) is most satisfactory. $NiCl_2 \cdot$DMP is known to exist as either the

(8) Electrochemically driven Cr(II)-mediated couplings are also known: (a) Grigg, R.; Putnikovic, B.; Urch, C. J *Tetrahedron Lett.* **1997**, *38*, 6307. (b) Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Tanaka, H.; Torii, S. *Tetrahedron Lett.* **1999**, *40*, 2785. (c) Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Tanaka, H.; Torii, S. *Synlett* **1999**, 69. (d) Durandetti, M.; Nedelec, J.-Y.; Perichon, J. *Org. Lett.* **2001**, *3*, 2073.

(9) For relevant studies on Cr-mediated couplings from this laboratory, see: (a) Reference 3a. (b) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343. (c) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386. (d) Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (e) Reference 4b. (f) Choi, H.-w.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1. (g) Reference 4c. (h) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031. (i) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417. (j) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421. (k) Reference 5c. (l) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073, and references cited therein.

(10) For chiral ligands used in Cr-mediated couplings, see: (a) Reference 3b. (b) *N*-Benzoylprolinol system: Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322. (c) Salen system: Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357. Bandini, M.; Cozzi, P. G.; Licciulli, S.; Umani-Ronchi, A. *Synthesis* **2004**, 409, and references cited therein. Also see: Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032. (d) Oxazoline/sulfonamide system: References 9c and 9f and references cited therein. (e) Bis(oxazolinyl)carbazole system: Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140. Inoue, M.; Suzuki, T.; Kinoshita, A.; Nakada, M. *Chem. Rec.* **2008**, *8*, 169, and references cited therein. Also see: McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551. Hargaden, G. C.; McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Org. Biomol. Chem.* **2007**, *5*, 763. (f) Oxazoline/prolineamide system: Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837. Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752. Also see: Hargaden, G. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, 4235. (g) Tethered bis(8-quinolinol): Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554; **2007**, *129*, 496.

Scheme 4. $NiCl_2$•DMP and CoPc-Assisted Activation of Halides[a]



[a] Panels A and B depict the proposed activation process of halides in the Ni/Cr- and Co/Cr-mediated couplings, respectively.

dimeric α-form or the monomeric β-form.[11] For this study, we use the α-form of $NiCl_2$•DMP, prepared and purified by the procedure given in the Supporting Information. It is also important to add LiCl, which significantly accelerates the coupling rate, most likely through formation of the Ni-ate complex (panel A in Scheme 4).[9e] The experimental details for the catalytic asymmetric Ni/Cr-mediated coupling are given in the Supporting Information.

Catalytic Cr-mediated alkylation and haloallylation are initiated by Co or Fe complexes.[9g] In our experience, Co(II) phthalocyanine (CoPc) is the most reliable catalyst for this purpose (panel B in Scheme 4). Mechanistically, we speculate an involvement of a free-radical species in this process, because an alkyl-Co(III) complex did not yield the expected coupling product.[12] Experimentally, it is important to keep the ratio of Co to Cr catalysts low. The experimental details of the catalytic asymmetric Co/Cr-mediated coupling are given in the Supporting Information.

It is worthwhile to note that the Ni- and Co-promoted activations are specific to the types of halides, and there is no crossover in the Ni- and Co-promoted activation. Therefore, it is possible to activate selectively one nucleophile in the presence of the other; the cases of C19−C20 and C23−C24 bond formation illustrate this point. On the other hand, with no addition of a Ni or Co salt, the active Cr nucleophiles are generated only from allyl and propargyl halides.

2. Results and Discussions

2.1. Strategy To Search for Effective Ligands. Recognizing their unique functional-group compatibility, we have been interested in development of a ligand-search strategy applicable to a broad range of substrates. With three distinct sites for structure modification, i.e., blue-, red-, and green-coded areas, **A** (Figure 2) provides us with access to structurally diverse chiral sulfonamides. We have synthesized several hundred sulfonamides with the hope that they might exhibit diverse reactivity profiles in Cr-mediated couplings, thereby allowing us to study

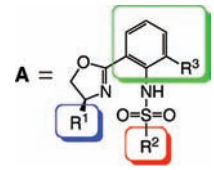
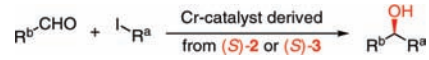


Figure 2. Generic structure of sulfonamide **A**.

Scheme 5. Absolute Configuration of the Alcohols Preferentially Formed in the Presence of the Cr Catalyst Derived from (*S*)-Sulfonamides



a broad range of substrates.[13] We first outline an effective strategy to search for a satisfactory ligand for a given substrate. Using the diverse C−C bond-forming cases selected from the halichondrin synthesis,[14] we then demonstrate that a satisfactory chiral ligand can indeed be found from this pool. For each of the cases studied, we deliberately search for two ligands, which induce the formation of (*R*)- and (*S*)-alcohols, respectively, with the arbitrarily chosen efficiency of "≥80% yield with ≥20:1 stereoselectivity in the presence of ≤20 mol % of a Cr catalyst".

Before discussing specific examples, we will make several general comments. First, the absolute configuration of alcohols formed through this process correlates to the absolute configuration of the ligand employed, i.e., R^1 group in **A**; in general, Cr catalysts derived from (*S*)-sulfonamides furnish secondary alcohols with the absolute configuration depicted in Scheme 5.[9e,f]

Second, in terms of asymmetric induction and coupling rate, the several hundred sulfonamides are divided into two subgroups, one represented by (*S*)-**2** and the other by (*S*)-**3** (Figure 3).[15,16] It is a general trend that couplings with the Cr catalysts derived from the **2** subgroup are faster than those with the Cr catalysts from the **3** subgroup, but asymmetric inductions with the former Cr catalysts are lower than those with the latter Cr catalysts. However, it is important to emphasize that the matching profiles, i.e., asymmetric induction and coupling rate, depend on a given substrate; some substrate exhibits a better matching profile with a Cr catalyst derived from a sulfonamide in the *i*-Pr subgroup than a Cr catalyst from a sulfonamide in the *t*-Bu subgroup or vice versa. For a given substrate, screenings with the Cr catalysts prepared from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3**

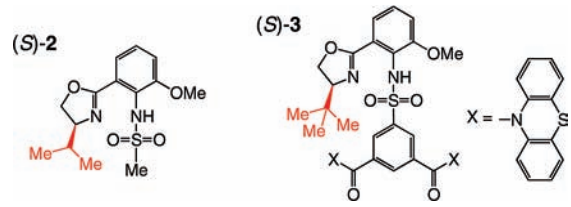


Figure 3. Structure of sulfonamides (*S*)-**2** and (*S*)-**3**.

(11) (a) Preston, H. S.; Kennard, C. H. L. *J. Chem. Soc. A* **1969**, 2682. (b) Butcher, R. J.; Sinn, E. *Inorg. Chem.* **1977**, *16*, 2334. (c) Dockum, B. W.; Reiff, W. M. *Inorg. Chem.* **1982**, *21*, 2613.

(12) This was done with a salen-Co(III)-alkyl complex at room temperature.

(13) The sulfonamides reported were prepared via a general synthetic route outlined in the Supporting Information. The details of their synthesis and reactivity profile will be disclosed in a separate account.

(14) Citations for the isolation, structure elucidation, and synthesis of the marine natural products halichondrins will be given in our forthcoming papers.[23]

(15) For the R^1 group, three subgroups of ligands, represented as R^1 = Me, *i*-Pr, and *t*-Bu, were studied. However, **2** represents reasonably well the reactivity profile for the R^1 = Me subgroup.

(16) The corresponding trimethoxylphenyl sulfonamide exhibits a profile very similar to that of **3**.[9i]

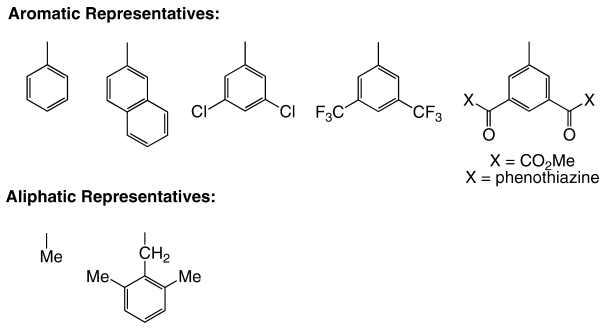


Figure 4. Representative aromatic and aliphatic R^2 groups in **A**.

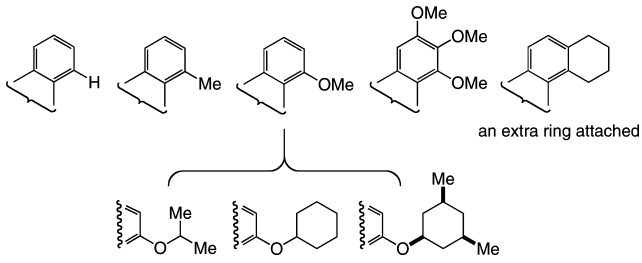


Figure 5. Representative R^3 groups in **A**.

shed light on two aspects of catalyst−substrate matching profile, i.e., (1) whether the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3** override the effects from the chirality present in a given substrate and (2) which subgroup of sulfonamides yields Cr catalysts with better catalyst−substrate matching profiles.

Third, for the R^2 group of **A**, we have studied a large number of aromatic and aliphatic sulfonamides, revealing the following. Aromatic sulfonamides are more effective in changing the overall matching profile of Cr catalysts for a given substrate than aliphatic sulfonamides. Representative aromatic sulfonamides are listed in Figure 4, with the (apparent) order of steric bulkiness. A given substrate often gives a bell-shaped optimum against the order of steric bulkiness of these aromatic sulfonamides.[17] Therefore, for a given substrate, we test first phenyl and 3,5-dichlorophenyl to obtain a rough catalyst−substrate matching profile for further ligand optimization. In addition, R^2 = Me and $CH_2Ph(Me)_2$-2,6 are chosen to test the effectiveness of ligand optimization within the aliphatic sulfonamides.

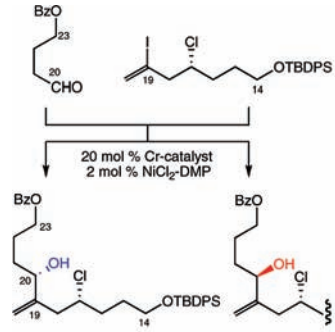
Fourth, for the R^3 group of **A**, we have made five types of structure modifications (Figure 5). Among them, Cr catalysts derived from the sulfonamides with R^3 = OR exhibited an interesting trend: replacement of the O-Me group with O-*i*-Pr, O-*c*-C_6H_{11}, or O-*cis,cis*-3,5-dimethylcyclohexyl results in a noticeable change of asymmetric induction without significantly affecting the coupling rate. As reported previously, the Cr catalysts derived from sulfonamides with R^3 = H perform well for 2-haloallylation and allylation.[9g,l]

With this background, we use the following examples to address two key questions. First, is the sulfonamide pool obtained through structure modification at the three sites of **A** large enough to match with a broad range of substrates? Second, is the outlined strategy effective to find a satisfactory ligand for a given substrate?

2.2. Examples. 2.2.1. C19−C20 Bond Formation. The first example is Ni/Cr-mediated coupling to form the C19−C20 bond

(17) Aromatic sulfonamides with electron-donating groups, as well as other substitution patterns, were tested, but they were not as effective as those shown in Figure 4.

Scheme 6. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C19−C20 Bond[19]



Ligands	*dr* (20α:20β)*
non-asymmetric	1.2:1
(*S*)-**2**	1:8.0
(*R*)-**2**	8.1:1
(*S*)-**3**	1:15
(*R*)-**3**	16:1
(*S*)-**4**	1:21
(*R*)-**4**	24:1

**dr* estimated by ^{1}H NMR (600 MHz)

of halichondrins (Scheme 6). Screening with the Cr catalysts prepared from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3** revealed that (1) all the Cr catalysts override the chirality present in the nucleophile and (2) all the Cr catalysts show a very small match/mismatch effect toward this chiral substrate, cf., *dr* with (*S*)-**2** over (*R*)-**2** and *dr* with (*S*)-**3** over (*R*)-**3**. The observed results of asymmetric induction itself might suggest using (*S*)-**3** and (*R*)-**3** as the leads for sulfonamide optimization. However, we noticed that the coupling rate with the Cr catalysts derived from (*S*)-**3** or (*R*)-**3** was slow—significantly slower than that with the Cr catalysts derived from (*S*)-**2** or (*R*)-**2**—thereby raising a concern about the overall efficiency of the catalytic process. For this reason, we decided to use (*S*)-**2** and (*R*)-**2** as the leads for sulfonamide optimization. Replacing R^2 = Me with R^2 = 3,5-Cl_2Ph or 3,5-$(CF_3)_2$Ph resulted in a significant improvement in stereoselectivity for both C20 β- and α-series. With the R^2 group being fixed with 3,5-Cl_2Ph and 3,5-$(CF_3)_2$Ph, a final refinement was then conducted on the R^3 group, yielding several satisfactory ligands.[18] In terms of asymmetric induction, they were very similar, but the Cr catalyst prepared from (*R*)-ligand **4** was best in terms of chemical yield. Coupling in the presence of the Cr catalyst derived from (*R*)- or (*S*)-ligand was very clean, selectively furnishing either the C20 α-alcohol (*dr* = 24:1) or the C20 β-alcohol (*dr* = 1:21) in >90% yields.

2.2.2. C29−C30 Bond Formation. The coupling depicted in Scheme 7 was originally achieved under stoichiometric nonasymmetric conditions.[20] Since then, this coupling was extended to a stoichiometric, asymmetric process[9c] and then to a catalytic asymmetric process.[9h]

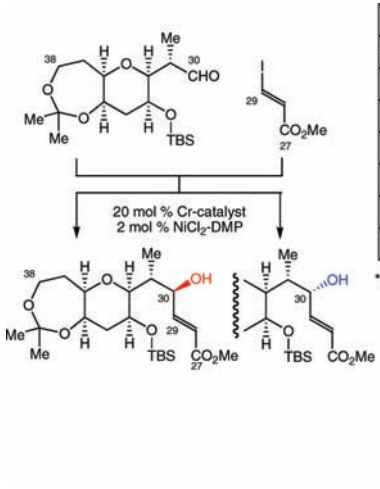
In this work, we first screened the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3**, revealing that (1) all the Cr catalysts override the chirality present in the substrate, (2) the Cr catalysts in the (*S*)-series of sulfonamides exhibit a better matching profile than the Cr catalysts in the (*R*)-series (cf., the *dr*'s observed for (*S*)-**2** and (*S*)-**3** over those for (*R*)-**2** and (*R*)-**3**, respectively), and (3) the Cr catalysts from (*S*)-**3** and (*R*)-**3**

(18) These include (*R*)-*i*-Pr/$PhCl_2$/OMe (*dr* = 21:1), (*R*)-*i*-Pr/$PhCl_2$/O-*i*-Pr (*dr* = 24:1), (*R*)-*i*-Pr/$PhCl_2$/O-*unnat*-menthol (*dr* = 22:1), (*R*)-*i*-Pr/$PhCl_2$/O-*c*-Hex (*dr* = 24:1), and (*R*)-*i*-Pr/$Ph(CF_3)_2$/O-*c*-Hex$(Me)_2$ (*dr* = 24:1).

(19) For the coupling conditions, see the Supporting Information.

(20) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549.

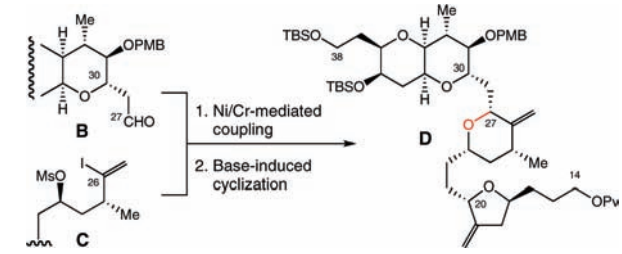
Scheme 7. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C29−C30 Bond[19]



Ligands	*dr* (30β:30α)*
non-asymmetric	1.1:1
(*S*)-**2**	7.2:1
(*R*)-**2**	1:4.8
(*S*)-**3**	*ca.* 37:1
(*R*)-**3**	1:6.4
(*S*)-**5**	*ca.* 60:1
(*R*)-**5**	*ca.* 1:27

**dr* estimated by ^{1}H NMR (600 MHz)

Scheme 8. Ni/Cr-Mediated Coupling Used in the First-Generation Synthesis of Halichondrins[6b]



give a greater asymmetric induction than the Cr catalysts from (*S*)-**2** and (*R*)-**2**, respectively (Scheme 7).

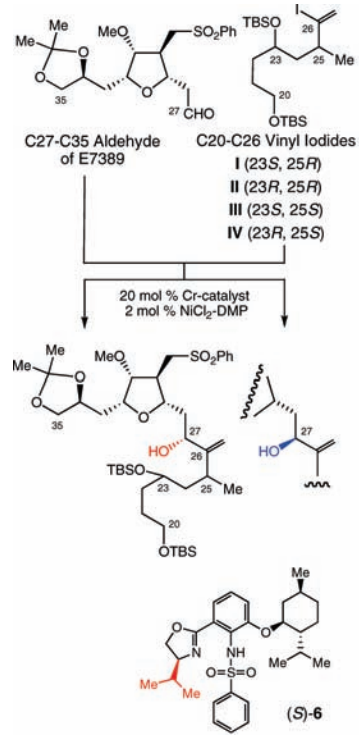
For a selective synthesis of the C30 β-alcohol, the Cr catalyst derived from (*S*)-**3** gave an asymmetric induction already well above the arbitrarily chosen level. In contrast, a Cr catalyst derived from either (*R*)-**2** or (*R*)-**3** failed to yield C30 α-alcohol at satisfactory selectivity, thereby requiring ligand optimization. As noted earlier, the Cr catalysts derived from the R^1 = *t*-Bu sulfonamide subgroup generally give a higher asymmetric induction than those from the R^1 = *i*-Pr sulfonamide subgroup. Unlike the case of C19−C20 bond formation, the coupling rate with the catalyst from (*R*)-**3** was not significantly slower than that from (*R*)-**2**. Therefore, we chose to conduct structure optimization of the R^2 and R^3 groups in (*R*)-**3**, in the usual stepwise manner, yielding ligand (*R*)-**5**; the catalyst derived from (*R*)-**5** gave C30 α-alcohol in >90% yield with satisfactory selectivity (*dr* = *ca.* 1:27). Notably, the catalyst from (*S*)-**5** was also found to improve the stereoselectivity for C30 β-alcohol formation (*dr* = *ca.* 60:1; >90% yield).[21]

2.2.3. C26−C27 Bond Formation. In the first-generation synthesis of halichondrins,[6b] we relied on the stoichiometric non-asymmetric Ni/Cr-mediated reaction to couple **B** and **C** (Scheme 8). A stoichiometric asymmetric version was then developed with use of the first-generation sulfonamide (*S*)-**1** (*dr* = 20:1).[9d,e]

This Ni/Cr-mediated coupling utilizes the electrophile and nucleophile bearing seven and four stereogenic centers, respectively, thereby presenting an interesting opportunity to study,

(21) For the C30 β-alcohol series, several additional sulfonamides, including (*S*)-*t*-Bu/$PhCl_2$/O-*c*-Hex(Me)$_2$ (*dr* = *ca.* 30:1), (*S*)-*i*-Pr/$PhCl_2$/O-*i*-Pr (*dr* = 21:1), and (*S*)-*i*-Pr/*3,5*-(CO-phenothiazine)$_2$Ph/OMe (*dr* = *ca.* 37:1), gave satisfactory Cr catalysts.

Scheme 9. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C26−C27 Bond[19]



	Ligands	*dr* (27α:27β)*
I	non-asymmetric	1.5:1
	(*S*)-**2**	*ca.* 36:1
	(*R*)-**2**	*ca.* 1:40
	(*S*)-**3**	*ca.* 32:1
	(*R*)-**3**	1:9.5
II	non-asymmetric	1.5:1
	(*S*)-**2**	14:1
	(*R*)-**2**	1:25
	(*S*)-**6**	*ca.* 47:1
	(*S*)-**3**	7.5:1
	(*R*)-**3**	1:11
III	non-asymmetric	1:1.7
	(*S*)-**2**	22:1
	(*R*)-**2**	*ca.* 1: 26
	(*S*)-**3**	5.0:1
	(*R*)-**3**	1:4.9
IV	non-asymmetric	1.5:1
	(*S*)-**2**	25:1
	(*R*)-**2**	*ca.* 1:100
	(*S*)-**3**	6.8:1
	(*R*)-**3**	1:5.2

**dr* estimated by ^{1}H NMR (600 MHz)

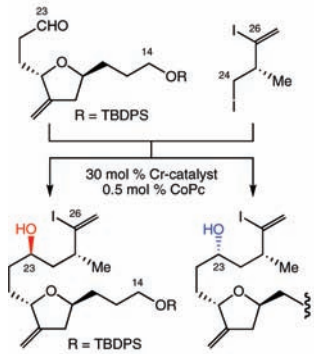
and validate, that the unique functional-group compatibility is maintained under the catalytic asymmetric conditions. Ideally, we wished to study the reactivity profile for all the stereoisomers possible for both coupling partners. However, considering the total number of possible stereoisomers, we opted to address this question by using the C27−C35 aldehyde of E7389 as the electrophile toward the nucleophiles representing all the possible stereoisomers at C20−C26, i.e., **I**−**IV**.

The standard screening with the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3** revealed that all the Cr catalysts override the substrate chirality in all of the combinations (Scheme 9). The observed degrees of asymmetric induction indicated that the Cr catalysts derived from (*S*)-**2** and (*R*)-**2** exhibit a better catalyst−substrate matching profile than that from (*S*)-**3** and (*R*)-**3**. In addition, the coupling rate was found to be significantly slower in the (*S*)-**3**/(*R*)-**3** series than in the (*S*)-**2**/(*R*)-**2** series. These observations suggested that (*S*)-**2** and (*R*)-**2** are better leads for sulfonamide optimization.

In the presence of the Cr catalysts derived from (*S*)-**2** and (*R*)-**2**, all the couplings proceeded smoothly to furnish the expected products in excellent yields and stereoselectivities; indeed, the arbitrarily chosen ≥20:1 stereoselectivity was met for 7 out of 8 possible substrate combinations. Ironically, the remaining combination was the one representing the stereoisomer required for the synthesis of halichondrins and E7389, i.e., substrate **II** with (*S*)-**2**. Therefore, ligand optimization was conducted for this combination with the usual procedure, thereby resulting in several satisfactory catalysts.[22] Among them, the Cr catalyst derived from ligand (*S*)-**6** was most effective (*dr* = *ca.* 47:1). In our forthcoming papers,[23] we use this catalyst for the key step in the synthesis of the C14−C38 building block of halichondrins as well as the C14−C35 building block of E7389.

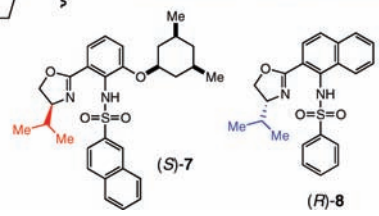
(22) (*S*)-*i*-Pr/$PhCl_2$/O-*i*-Pr also gave the satisfactory result (*dr* = *ca.* 26:1).

Scheme 10. Catalytic Asymmetric Co/Cr-Mediated Couplings To Form the C23−C24 Bond[19,24]



Ligands	*dr* (23β:23α)*
non-asymmetric	2.5:1
(*S*)-**2**	9.9:1
(*R*)-**2**	1:3.7
(*S*)-**3**	8.4:1
(*R*)-**3**	1:1.8
(*S*)-**4**	*ca.* 33:1
(*S*)-**7**	22:1
(*R*)-**8**	1:8.1

*dr estimated by ^{1}H NMR (600 MHz)

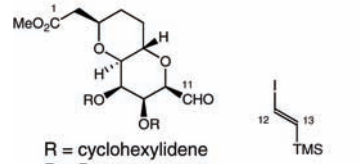


2.2.4. C23−C24 Bond Formation. In this coupling (Scheme 10), selective activation of the alkyl iodide bond over the vinyl iodide bond is achieved with a catalytic amount of Co phthalocyanine (CoPc).[9e] Using the Cr catalyst prepared from the first-generation sulfonamide (*S*)-**1**, we demonstrate its feasibility under catalytic asymmetric conditions (73% yield; *dr* = 5.3:1).

With this background, we screened the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3**, thereby revealing that (1) all the Cr catalysts override the effects of the chirality present in both nucleophile and electrophile and (2) the Cr catalysts derived from (*S*)-**2** and (*R*)-**2** exhibit a better substrate matching profile than those from (*S*)-**3** and (*R*)-**3**.[24] Using (*S*)-**2** as the lead, we conducted ligand optimization first for the C24 β-alcohol series, yielding several satisfactory sulfonamides; the Cr catalyst derived from ligand (*S*)-**4** (Scheme 6) was most effective for the asymmetric induction (ca. 33:1), but the Cr catalyst from ligand (*S*)-**7** was best in asymmetric induction (*dr* = 22:1) and yield (82%) combined.[25]

It was significantly more challenging to find a satisfactory Cr catalyst for the C24 α-alcohol series. Using (*R*)-**2** as the lead,[26] we performed ligand optimization, resulting in modest improvement; for example, an (*R*)-sulfonamide with R^1 = *i*-Pr, R^2 = 3,5-Cl_2Ph, and R^3 = OMe gave *dr* = 1:6.2. Under this circumstance, we decided to conduct a broader structural modification, through which ligand (*R*)-**8** emerged as the leading ligand (*dr* = 1:8.1).[27] However, its optimization has not yet yielded a sulfonamide to meet the arbitrarily chosen standard.

Scheme 11. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C11−C12 Bond[19]



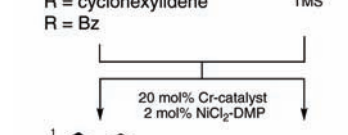
Cyclohexylidene Series

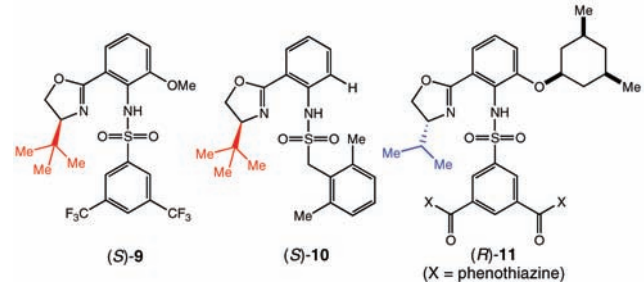
Ligands	*dr* (11β:11α)*
non-asymmetric	2.0:1
(*S*)-**2**	*ca.* 42:1
(*R*)-**2**	4.6:1
(*S*)-**3**	6.8:1
(*R*)-**3**	1.5:1
(*S*)-**9**	*ca.* 80:1
(*R*)-**9**	10:1

Bisbenzoate Series

Ligands	*dr* (11β:11α)*
non-asymmetric	1.5:1
(*S*)-**2**	12:1
(*R*)-**2**	1:2.6
(*S*)-**3**	2.3:1
(*R*)-**3**	1:1.7
(*S*)-**10**	*ca.* 56:1
(*R*)-**11**	1:23

*dr estimated by ^{1}H NMR (600 MHz)





2.2.5. C11−C12 Bond Formation. The transformation summarized in Scheme 11 was originally used under stoichiometric non-asymmetric conditions, to furnish the desired C11 β-alcohol in 75% yield with >10:1 stereoselectivity.[6b]

With use of the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3**, we conducted a standard catalyst screening, revealing that the Cr catalysts derived from (*R*)-**2** or (*R*)-**3** *cannot* override the effects from the chirality present in the aldehyde. Given the high stereoselectivity observed under the stoichiometric non-asymmetric conditions, we were not surprised by the observed catalyst−substrate matching profile. Overall, the observed catalyst−substrate matching profile predicted that ligand optimization might be relatively straightforward for the C11 β-alcohol series but challenging for the C11 α-alcohol series.

For the C11 β-alcohol series, considering the stereoselectivity achieved in the presence of the Cr catalyst from (*S*)-**2** over that from (*S*)-**3**, we first used (*S*)-**2** as the lead for ligand optimization, yielding several acceptable ligands,[28] but none of them performed better than (*S*)-**2** (*dr* = *ca.* 42:1). Intriguingly, optimization of (*S*)-**3** resulted in the best ligand, (*S*)-**9**: in the presence of its Cr complex, the coupling gives the desired C11 β-alcohol virtually as a single diastereomer quantitatively.

(23) (a) Kim, D.-S.; Dong, C.-G.; Kim, J. T.; Guo, H.; Huang, J.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, in press (ja9058475). (b) Dong, C.-G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D.-S.; Kim, J. T.; Urabe, D.; Guo, H.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, in press (ja9058487) .

(24) For the Co/Cr-mediated coupling, it is important to keep the ratio of Co and Cr catalysts low. To measure an amount of CoPc with an acceptable accuracy, we used 30 mol % of Cr catalyst for this screening. For preparative purposes, 20 mol % catalyst loading was sufficient to effect this coupling.

(25) These include (*S*)-*i*-Pr/Ph(CF_3)$_2$/O-*c*-Hex(Me)$_2$ (*dr* = *ca.* 32:1), (*S*)-*i*-Pr/PhCl_2/benzo-1,4-dioxane (*dr* = *ca.* 26:1), (*S*)-*i*-Pr/Ph-(CO_2Me)$_2$/Me (*dr* = *ca.* 25:1), (*S*)-*i*-Pr/3,5-(CO-phenothiazine)$_2$Ph/Me (*dr* = 25:1), and (*S*)-*i*-Pr/2-naphthyl/O-*c*-Hex(Me)$_2$ (*dr* = 22:1).

(26) For this ligand optimization, we used also the first-generation (*R*)-sulfonamide (R^1 = *i*-Pr, R^2 = Me, and R^3 = Me; *dr* = 1:1.9) as the lead, resulting in a modest improvement; for example, *dr* = 1:2.5 was observed for the catalyst from (*R*)-*i*-Pr/2-naphthyl/*i*-Pr.

(27) Several sulfonamides, including (*R*)-*i*-Pr/PhOMe-*p*/naphthyl (*dr* = 1:8.0) and (*R*)-*i*-Pr/2-naphthyl/naphthyl (*dr* = 1:7.4), gave approximately the same level of asymmetric induction as ligand (*R*)-**8**.

(28) These include (*S*)-*i*-Pr/Ph(CF_3)$_2$/OMe (*dr* = *ca.* 29:1), (*S*)-*i*-Pr/PhCl_2/OMe (*dr* = *ca.* 28:1), and (*R*)-*i*-Pr/PhCl_2/O-*i*-Pr (*dr* = 24:1).

As predicted, it proved a major challenge to override the chirality inherent in the aldehyde; despite extensive efforts, we were unable to find a Cr catalyst for the coupling to yield the C11 α-alcohol as the major product.[29] With these results, we turned our attention to the catalyst−substrate matching profile for the same aldehyde but bearing different protecting groups. Namely, we became interested in testing whether the Cr catalysts derived from (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, and (*R*)-**3** could override the chirality inherent in the aldehyde with a minor structural modification. Thus, aldehydes bearing the acetonide, bis-methoxymethyls (MOMs), and bis-*tert*-butyldimethylsilyls (TBSs) were studied, without any sign of success until the bisbenzoate aldehyde was tested. To our delight, this substrate exhibited the long-awaited catalyst−substrate matching profile: the C11 α-alcohol was the major product formed in the presence of the Cr catalyst from (*R*)-**2** and (*R*)-**3**, whereas the C11 β-alcohol was the major product in the presence of the Cr catalyst from (*S*)-**2** and (*S*)-**3** (Scheme 11).

Encouraged by this result, we conducted standard ligand optimization. For the C11 β-alcohol series, we first used (*S*)-**2**, rather than (*S*)-**3**, as the lead. In parallel with the cyclohexylidene series, however, the best ligand, (*S*)-**10** (*dr* = *ca*. 56:1), emerged again from the ligand optimization of (*S*)-**3**. For the C11 α-alcohol series, considering both the observed asymmetric induction and coupling rate, we used (*R*)-**2** as the lead for ligand optimization. Through this effort, (*R*)-sulfonamide **11** was found as a satisfactory ligand (*dr* = 1:23).[30]

3. Conclusion and Outlook

In summary, catalytic asymmetric Cr-mediated couplings are effected by catalysts prepared from $CrCl_2$ and chiral sulfonamides represented by **A**. With three distinct sites for structure modification, **A** provides access to structurally diverse chiral sulfonamides. The Cr catalysts derived from these sulfonamides exhibit a broad range of catalyst−substrate matching profiles, suggesting the possibility that this class of sulfonamide-based catalysts could match with diverse substrates. A strategy has been presented to search for a satisfactory sulfonamide for a given substrate. In order to demonstrate the *generality and effectiveness* of this approach, we have used five diverse C−C bond-forming cases from the halichondrin synthesis. For each of the cases studied, we have deliberately searched for two ligands, which induce the formation of (*R*)- and (*S*)-alcohols, respectively, at the arbitrarily chosen efficiency level of "≥80% yield with ≥20:1 stereoselectivity in the presence of ≤20 mol % of a Cr catalyst". For 9 out of the 10 cases studied, we have been able to find a satisfactory catalyst. Even for the remaining case, we have found a Cr catalyst inducing stereoselectivity up to 8:1. Encouraged by the successful case studies on structurally diverse substrates, we have developed an optimistic prospect for this approach. In our forthcoming papers,[23] we will report that these catalytic asymmetric Cr-mediated couplings have major impacts on the syntheses of halichondrins and E7389; the newly developed methods allow us to form the key carbon−carbon bonds in a highly stereoselective manner, improve the overall synthetic efficiency, reduce the total number of synthetic steps, and also incorporate a high degree of flexibility in synthesis.

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Supporting Information Available: Experimental details, including syntheses of the substrates for the coupling reactions and chiral sulfonamides, estimation of the diastereomer ratios by ^{1}H NMR, and synthesis/characterization of the chiral sulfonamides. This material is available free of charge via the Internet at http://pubs.acs.org.

JA905843E

(29) Interestingly, *trans*-1-iodohex-1-ene exhibits a similar catalyst−substrate profile.

(30) For this optimization, we studied sulfonamides in the R^1 = Me subgroup. Some of them, e.g., (*R*)-Me/$PhCl_2$/O-*c*-Hex$(Me)_2$ (*dr* = 1:15), exhibited a promising matching profile, but their overall behavior was found to be similar to that of R^1 = *i*-Pr subgroup sulfonamides.