Review

Catalytic Asymmetric Friedel#Crafts Alkylation Reactions#Copper Showed the Way

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Catalytic Asymmetric Friedel−Crafts Alkylation Reactions—Copper Showed the Way

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1. Introduction

1.1. Historical Background

Charles Friedel (1832−1899) started a dual scientific career and spent several years of activities divided between mineralogy at Ecole des Mines and chemical research.[1] The early research carried out by Friedel, under the direction of Wurts, included studies on ketones, lactic acid, and organosilicon compounds. When James Mason Crafts (1839−1917), a mining engineer from Boston, arrived for a period of study under Wurts in 1861, the two men—Friedel and Crafts—created an immediate friendship. Realizing that they had many ideas in common, they decided to undertake a research partnership, and in the period of 1863−1865, they made a number of joint studies on various organic compounds of silicon.

When Crafts departed from Paris in 1865, Friedel continued his research in both chemistry and mineralogy; however, his career was interrupted by the Franco-Preussian war in 1870. Crafts returned to the United States, and he was in 1867 chosen as a professor at Cornell University and moved to MIT in 1870. In 1874, ill health forced him to go abroad, and he returned to Paris to continue research with Friedel in various areas of chemistry. Crafts anticipated that he would be in France for 2−3 years; however, the discovery of the Friedel−Crafts reaction in 1877 resulted in such profile research that Crafts remained in Paris for 17 years. Friedel and Crafts, their co-workers, and students published close to a hundred scientific papers, not only on the aluminum chloride reaction but also in other fields.

Surprisingly, although Friedel and Crafts are best remembered by the reaction that bears their names, their work on the use of aluminum chloride in organic synthesis played a comparatively minor role in their lives. Both rendered pioneering service to the development of the chemical sciences and left a distinctive mark of their outstanding personalities to future generations.[1]

Now—130 years later—the Friedel−Crafts reaction is one of the important cornerstones in chemistry, and its use has had, and still has, an enormous impact on chemistry and society.

1.2. Reactions Covered and Catalytic Principle

Friedel−Crafts reactions can in a generalized sense be divided into alkylations and acylations.[2] In this review, only the alkylation of aromatic and heteroaromatic compounds, in which a hydrogen atom is replaced by an alkyl group, will be considered.[3] The alkylation reagents will include activated alkenes, carbonyl compounds, and imines, and Scheme 1 presents the reactions to be discussed in the following. Furthermore, we will also briefly present the catalytic enantioselective Friedel−Crafts alkylation with epoxides and allyl electrophiles.

The Friedel−Crafts reaction requires a catalyst to proceed, and the traditional catalysts include Lewis acids such as $AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$, and $TiCl_4$; Brønsted acids such as HF, H_2SO_4, and H_3PO_4; and acidic oxide catalysts of, for example, silica−alumina type and cation-exchange resins.[1b]

To form optically active compounds based on Friedel−Crafts alkylation reactions, one can either employ an optically active catalyst/mediator or perform diastereoselective reactions using chiral substrates followed by cleavage of the auxiliary. In this review, we will focus on catalytic asymmetric Friedel−Crafts alkylation reactions.

As will be apparent in the following, two of the successful strategies for performing catalytic enantioselective Friedel−Crafts alkylation reactions have been developed directly from the traditional catalysts used for the Friedel−Crafts reaction. The first of these involves the use of chiral Lewis acids, in which a chiral ligand is coordinated to the Lewis acid, and

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Karl Anker Jørgensen received his Ph.D. from Aarhus University in 1984. He was a postdoc with Professor Roald Hoffmann, Cornell University, in 1985. In 1985, Dr. Jørgensen became assistant professor at Aarhus University and became professor at the same place in 1992. His research interest is the development, understanding, and application of asymmetric catalysis.

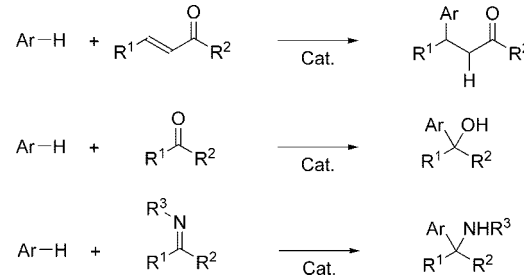
the second involves the use of chiral Brønsted acids. The activation of the electrophilic reagent by such catalysts is based on the interaction of the Lewis or Brønsted acidic site with oxygen or nitrogen lone-pair electrons in the reagent, thereby increasing its electrophilic character, making it more prone to react with the aromatic substrate. These two similar activation strategies rely on noncovalent interactions between the chiral catalyst and the reagent. A third type of activation, based on covalent interactions, has also been used with success in Friedel−Crafts alkylations. In this case, the catalyst—a chiral primary or secondary amine—reacts with an α,β-unsaturated carbonyl compound, forming an iminium intermediate, in which the β-position is activated for nucleophilic attack by the aromatic compound.

1.3. The Development of Catalytic Asymmetric Friedel−Crafts Alkylation Reactions

Figure 1 shows a graphical presentation of the number of papers published per year since 1990 in the field of catalytic asymmetric Friedel−Crafts alkylation reactions.

Several things are apparent when inspecting this diagram: (i) Until approximately 1999−2000, there were only isolated

Scheme 1. Three Different Alkylation Reactions Primarily Considered in the Review



reports describing catalytic asymmetric Friedel−Crafts alkylation reactions. Since this time, activities have been increasing tremendously. (ii) Copper-based catalysts have played a privileged role, in particular in the early years. (iii) Organocatalytic methods are becoming increasingly important.

As this issue of Chemical Reviews is devoted to coinage metals, we will in this review focus primarily on the use of such a metal—copper—as a catalyst for Friedel−Crafts alkylation reactions. The reason for focusing on copper is that this metal was until very recently the only coinage metal applied for these catalytic asymmetric transformations. However, within the last year, the application of gold and platinum has also been introduced to catalytic asymmetric Friedel−Crafts alkylation reactions as discussed in the final part of the review. We will, but to a smaller extent, also present other contributions to the field, that is, the use of other metal complexes and organocatalysis in an attempt to put mainly the copper-catalyzed reactions into perspective. As almost one-third of all papers published concerning catalytic asymmetric Friedel−Crafts alkylation reactions involves the use of a copper complex, this bias is to a large extent justified, but we do apologize to the authors who may feel that their contributions have not been given the appropriate space. We have, however, aimed for the review to be a comprehensive overview of the literature; therefore, we will also include enantioselective alkylation reactions for which a copper-based catalyst system has not been reported.

2. The Incubation Period

As mentioned above, until 1999, the contributions to the field of catalytic asymmetric Friedel−Crafts alkylation reactions were somewhat sporadic. The importance of these

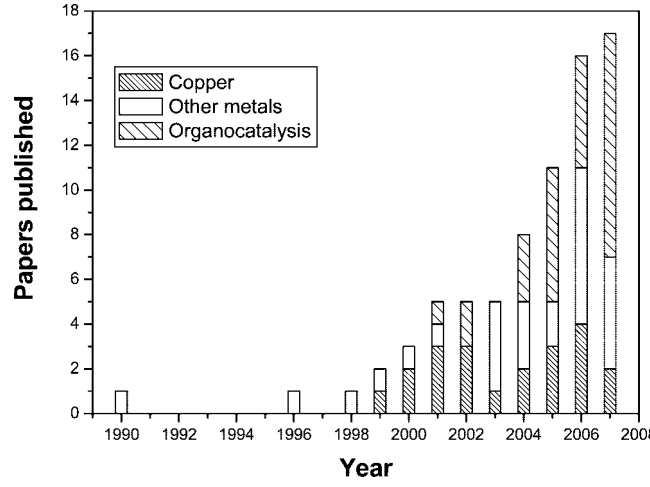
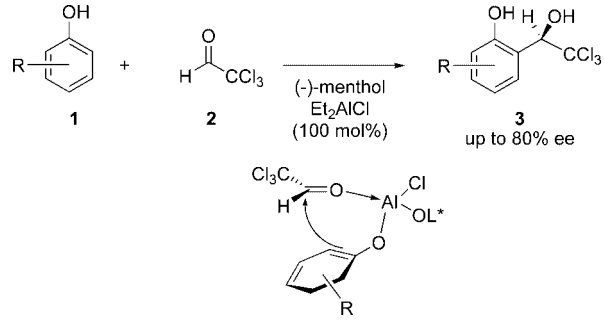
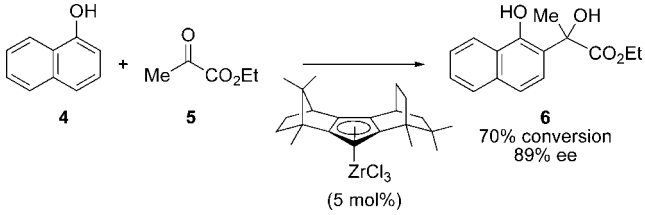


Figure 1. Catalytic asymmetric Friedel−Crafts alkylation reactions—papers published 1990−2007.

Scheme 2. Enantioselective *ortho*-Hydroxyalkylation of Phenols by Chloral Mediated by Et_2AlCl-(−)-menthol



Scheme 3. Enantioselective Hydroxyalkylation of 1-Naphthol Using Ethyl Pyruvate Catalyzed by a $ZrCl_3$-Dibornacyclopentadienyl Complex



pre-1999 studies is of course enormous in the sense that they laid the foundation for the field as we know it today. Furthermore, the selectivities reported were impressive when compared to the standards at the time.

In 1985, Casiraghi et al.[3] introduced the enantioselective *ortho*-hydroxyalkylation of phenols **1** by chiral alkoxyaluminum chlorides. In their search for a modified Lewis acid to promote the enantioselective electrophilic substitution of phenols, they discovered that stoichiometric amounts of chiral alkoxyaluminum chlorides obtained from Et_2AlCl and chiral alcohols could promote the desired reaction (Scheme 2). Menthol was found to be the best ligand, and for substituted phenols **1** reacting with chloral **2**, the asymmetric Friedel−Crafts hydroxyalkylation took place in moderate yield and up to 80% ee of the chiral alcohol **3** in the case of 2,5-dimethyl phenol. To account for the stereoinduction and regioselectivity, a chelate transition state model as outlined in Scheme 2 was proposed.

A hard chiral Lewis acid complex was also used by Erker et al. for the first catalytic enantioselective Friedel−Crafts alkylation with carbonyl compounds.[4] Using 1-naphthol **4** as the aromatic nucleophile, the reaction with ethyl pyruvate **5** afforded the corresponding optically active alcohol **6** in 89% ee and in 70% conversion (Scheme 3). The chiral catalyst was a $ZrCl_3$−dibornacyclopentadienyl complex, of which the chiral ligand was prepared from (+)-camphor in a few steps.

An asymmetric Friedel−Crafts reaction was also developed by Nakagawa et al.[5] in their studies of reagent-controlled enantioselective Pictet−Spengler type reactions of nitrones derived from the condensation of *N*-hydroxytryptamine with aldehydes. The application of (+)-Ipc_2BCl as the mediator for this reaction gave up to 91% ee.

From 1999, when the use of copper complexes for the asymmetric aza-Friedel−Crafts reaction was introduced,[6] a significant increase has taken place in catalytic enantioselective Friedel−Crafts alkylation reactions using chiral coinage complexes, other chiral metal complexes, and small organic catalysts—organocatalysis.

3. Alkylation with Activated Alkenes

3.1. Copper Complexes

The first system developed for catalytic enantioselective Friedel−Crafts alkylation with alkenes was based on copper.[7] The reason for using copper as the Lewis acid catalyst for the alkylation of β,γ-unsaturated-α-ketoesters was based on the successful use of especially Cu(II)-bisoxazolines (BOX) as catalysts for a number of different stereoselective reactions for a large variety of substrates.[8] The strategy for using the Cu(II)-BOX, and the chiral Cu(II)-ligand complexes developed later, for the Friedel−Crafts alkylation of alkenes was that these should include functional groups that are able to coordinate in a mono- or bidentate fashion to the chiral catalyst. This requires that the substrate has one or two Lewis basic sites, found in, for example, β,γ-unsaturated-α-ketoesters and alkylidene malonates, which can coordinate to the chiral copper complex such as Cu(II)-*tert*-Bu-BOX in a bidentate fashion, as shown in Figure 2.

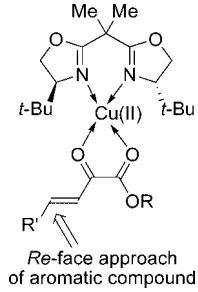
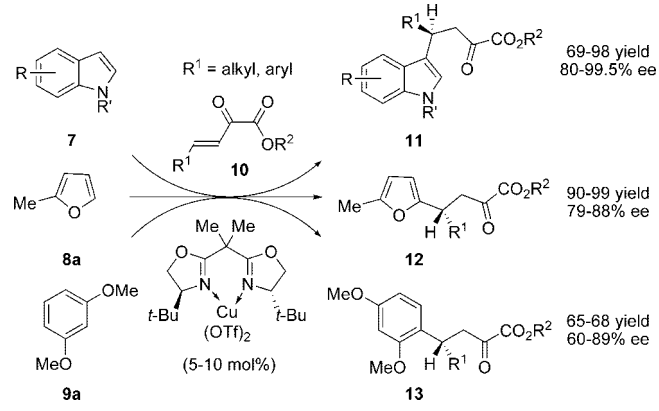


Figure 2. Bidentate coordination of β,γ-unsaturated-α-ketoesters to Cu(II)-*tert*-Bu-BOX.

The Friedel−Crafts alkylation of β,γ-unsaturated-α-ketoesters **10** was shown to take place for a number of heteroaromatic and aromatic compounds using 5−10 mol % $Cu(OTf)_2$-*t*-Bu-BOX as the catalyst. The indoles **7** gave the best enantioselectivities and up to >99.5% ee of the corresponding optically active products **11** were obtained, while for 2-methyl furan **8a** and electron-rich benzenes, such as 1,3-dimethoxybenzene **9a**, the yields and enantiomeric excesses of the corresponding optically active Friedel−Crafts products, **12** and **13**, respectively, were lower than for the indoles (Scheme 4). The absolute configurations of the products formed were in accordance with the model shown in Figure 2 in which the *Si* face of the alkene part of the

Scheme 4. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles, 2-Methyl Furan, and 1,3-Dimethoxybenzene with β,γ-Unsaturated-α-ketoesters Catalyzed by $Cu(OTf)_2$-*t*-Bu-BOX

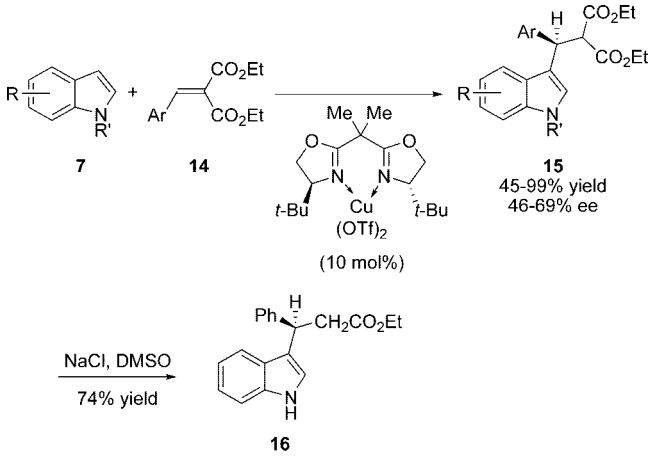


β,γ-unsaturated-α-ketoesters is shielded by the *tert*-butyl substituent of the chiral copper catalyst primarily allowing the heteroaromatic and aromatic compound to approach the γ-carbon atom in the β,γ-unsaturated-α-ketoester from the *Re*-face.

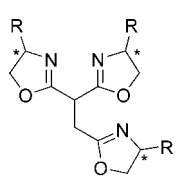
After this first demonstration of copper-catalyzed Friedel−Crafts alkylation with activated alkenes, a number of papers appeared, and in the beginning, the focus was on further developing the catalysts and expanding the type of alkenes that would undergo stereoselective addition.

Alkylidene malonates were the next substrate type submitted for asymmetric Friedel−Crafts alkylation using chiral copper complexes as the catalyst (Scheme 5).[9] Diethyl arylidene malonates **14** were chosen as substrates for the reaction with heteroaromatic compounds, and although the reaction proceeded in excellent yields, the enantiomeric excesses of the optically active alkylated indoles **15** were only moderate (up to 69% ee). For the optically active indole products **15**, it was demonstrated that these could undergo a Krapcho type decarboxylation reaction to give the monoester **16**.

Scheme 5. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles with Diethyl Arylidene Malonates Catalyzed by Cu(OTf)$_2$-*t*-Bu-BOX



In a series of papers by Tang et al.,[10] a chiral coinage Lewis acid complex—also based on Cu(II)—for the Friedel−Crafts alkylation of indoles with alkylidene malonates was developed. The major contribution was the introduction of trisoxazoline **17** as the chiral ligand, rather than the bisoxazoline, for this reaction. It should also be noted that the same group showed that removal of one of the methyl groups at the carbon bridging the oxazoline groups in the bisoxazolines also led to a significant improvement of the enantioselectivity (up to 93% ee for arylidene malonates, while for ethylidene malonate 60% ee was obtained).[10a,c]



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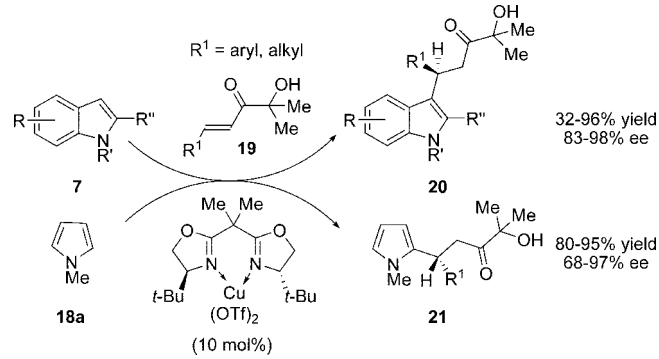
The trisoxazoline motif turned out to be a good choice for improving the enantioselectivity of the Cu(II)-catalyzed Friedel−Crafts alkylation of alkylidene malonates with

Scheme 6. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles and *N*-Methyl Pyrrole with α′-Hydroxy-enones Catalyzed by Cu(OTf)$_2$-*t*-Bu-BOX



indoles.[10a,b,d] For the trisoxazoline having *iso*-propyl substituents at the stereocenters, the enantioselectivity could be improved to 98% ee. The Tang group did a thorough investigation of a number of parameters, such as solvents, additives, ratio of ligand/copper, catalyst loading, reaction temperature, ligands, variation in indoles, alkylidene malonates, and labeling studies. A number of important observations surfaced from these studies; in *iso*-butyl alcohol, the Friedel−Crafts alkylation product could be obtained in excellent yields and with up to +98% ee, while in 1,1,2,2-tetrachloroethane the opposite enantiomer of the product was formed in good yields and with up to −89% ee. This catalytic system of the trisoxazolines and Cu(OTf)$_2$ turned out to be water-tolerant; for example, 200 equiv of water relative to the catalyst in *iso*-propyl alcohol had almost no effect on the enantioselectivity, although it did decrease the rate of the reaction.

It was later demonstrated by Reiser et al.[11] that the use of a Cu(II)-aza-BOX complex could improve the enantioselectivity of the standard reaction of diethyl benzylidene malonate with indoles, outlined in Scheme 5, to be >99% ee, provided that an excess of chiral ligand relative to copper was avoided. Furthermore, it was also shown that ethenetricarboxylates are useful substrates for Friedel−Crafts alkylation with indoles when applying 10 mol % of Cu(OTf)$_2$-*t*-Bu-BOX as the catalyst.[12]

An important extension of the Friedel−Crafts alkylation with alkenes was presented by Palomo et al.,[13] who showed that highly enantioselective alkylation of indoles **7** and pyrroles **18** with α′-hydroxy-enones **19** under Cu(II)-BOX catalysis was possible (Scheme 6). *N*-Methyl pyrrole **18a** reacted smoothly with mainly alkyl-substituted α′-hydroxy-enones, and the corresponding optically active Friedel−Crafts pyrrole adducts **21**were obtained in high yields and excellent enantioselectivities, while slightly lower enantioselectivity (68% ee) was obtained for an aromatic α′-hydroxy-enone (R^1 = Ph). With indoles, the reaction also proceeded very well, and similar results as for the pyrroles were obtained. The authors also demonstrated that it was possible to transform the Friedel−Crafts alkylation products **20** and **21**, formed by reaction of **7** and **18a**, to the corresponding optically active aldehydes, carboxylic acids, and ketones by standard elaborations of the α′-hydroxy-carbonyl functionality.

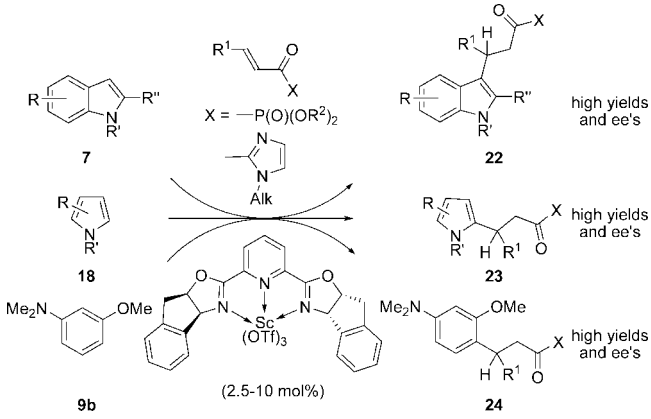
Indoles were also the aromatic reagent for the Friedel−Crafts alkylation with nitroalkenes[14] and α′-phosphoric enones[15] with Cu(II)-BOX complexes as the catalyst. The Friedel−Crafts alkylation of indoles with nitroalkenes was demonstrated for a number of aromatic nitroalkenes, and the

corresponding optically active products were obtained in moderate to good yields and enantioselectivities. Unfortunately, no details were provided on how the chiral copper complex activated and achieved face selectivity of the nitroalkene. The α′-phosphoric enones also gave good results in terms of both yield and enantioselectivity by the reaction with indoles in the presence of an indane-Cu(OTf)$_2$-BOX as the catalyst. Kim et al.[15] also showed that the optically active β-keto phosphonates could be converted to the corresponding ketones without loss of optical purity.

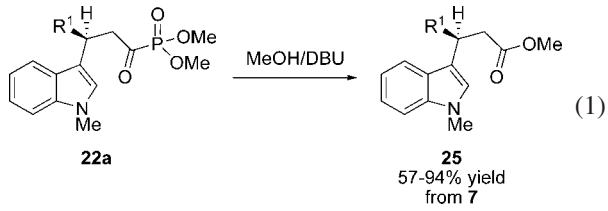
3.2. Other Metal Complexes

Evans et al.[17] have in a series of papers shown that a Sc(III)-bis(oxazolinyl)pyridine complex is an effective catalyst for the Friedel−Crafts alkylation of indoles **7**, pyrroles **18**, 3-dimethylaminoanisole **9b**, and 2-methoxyfuran with β-substituted-α,β-unsaturated 2-acyl phosphonates and α,β-unsaturated 2-acyl imidazoles (Scheme 7). These reactions were developed to proceed in high yields and with enantioselectivities >90% ee.

Scheme 7. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles, Pyrroles, and 3-Dimethylaminoanisole with β-Substituted-α,β-unsaturated 2-Acyl Phosphonates and α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by a Sc(III)-Bis(oxazolinyl)pyridine Complex



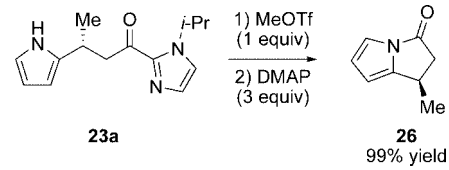
An important aspect of the application of the β-substituted-α,β-unsaturated 2-acyl phosphonates and α,β-unsaturated 2-acyl imidazoles as substrates for these Friedel−Crafts alkylation reactions is that it is possible, for example, for the intermediate β-indolyl 2-acyl phosphonates **22a** to convert them directly into the corresponding methyl esters **25** by direct addition of MeOH and DBU to the reaction mixture (eq 1).



(1)

A number of other transformations were also presented, such as the formation of the optically active 2,3-dihydro-1*H*-pyrrazoline **26** formed by treatment of the pyrrole adduct **23a** with MeOTf followed by base such as DMAP (eq 2).

Another coinage metal—silver—was indirectly used for the preparation of a Pd(II)-BINAP catalyst for the asymmetric

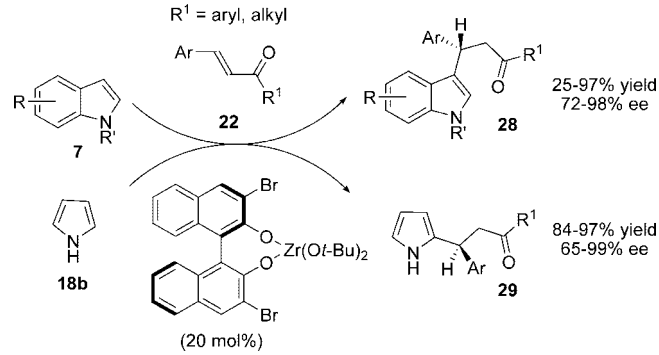


(2)

Friedel−Crafts alkylation of indoles with α,β-unsaturated *S*-acyl sulfanyl-1,3-benzoxazoles as developed by Bandini and co-workers.[17] During the screening process, another chiral coinage metal complex—Cu(I)/(II)-BINAP—was also tested; however, the Pd(II)-BINAP complex gave the best results with up to 80% yield and 86% ee for different substituted indoles. The same authors[18] also showed that chiral Al(III)-salen complexes could catalyze the enantioselective Friedel−Crafts alkylation of (*E*)-arylcrotyl ketones with indoles to give the corresponding β-indolyl ketones in high yields and enantioselectivities up to 89% ee.[18a,b] Aromatic nitroalkenes were also shown to react with indoles; however, lower enantioselectivity was obtained as compared to the enones. The latter approach provided precursors for enantiomerically enriched tryptamine precursors.[18c]

For the asymmetric Friedel−Crafts alkylation of simple enones, a highly enantioselective approach was developed by Blay et al., who showed that a chiral Zr(IV)-BINOL complex could catalyze the addition of both indoles **7** and pyrrole **18b** to a large number of β-aryl α,β-enones **22**, as shown in Scheme 8.[19] Both indoles and pyrrole gave for the majority of the substrates excellent yields and enantioselectivities >90% ee of the corresponding products **28** and **29**, respectively. Furthermore, Bandini et al. have demonstrated an intramolecular version of a related reaction with up to 60% ee.[20]

Scheme 8. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles and Pyrroles with β-Aryl α,β-Enones Catalyzed by a Zr(IV)-BINOL Complex



Finally, it should also be noted that Zn(II)-BOX complexes have been used for the asymmetric Friedel−Crafts alkylation of indoles with nitroalkenes and enantioselectivities up to 98% ee were obtained in the best case.[21]

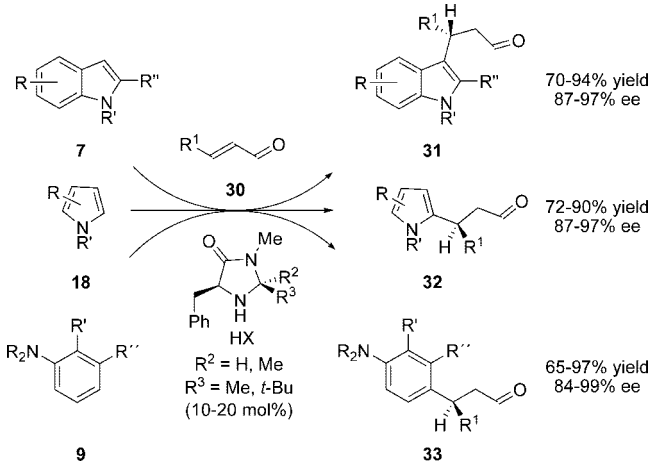
3.3. Organocatalysis

Although, not based on chiral coinage metal catalysis, not even chiral metal catalysis, organocatalysis as a tool for enantioselective Friedel−Crafts alkylation reactions with activated alkenes will also briefly be presented here.

The first contribution to organocatalytic enantioselective Friedel−Crafts alkylation was presented by MacMillan et al.[22] who, in a series of papers, developed the reactions of indoles **7**, pyrroles **18**, and electron-rich benzenes **9** with α,β-

unsaturated aldehydes **30** (Scheme 9). For all three systems, the reaction conditions and catalysts were optimized to give the Friedel−Crafts alkylation products **31**−**33** in high yields and generally with enantioselectivities >90% ee.

Scheme 9. Organocatalytic Eenantioselective Friedel−Crafts Reaction of Indoles, Pyrroles, and Electron-Rich Benzene Derivatives with α,β-Unsaturated Aldehydes Using Chiral Imidazolidinones as the Catalyst



Organocatalytic Friedel−Crafts reactions have also been part of asymmetric cascade processes in which a heteroaromatic compound was added to the β-position of the α,β-unsaturated aldehyde via an iminium mechanism, followed by electrophilic chlorination or fluorination, now by an enamine mechanism.[23] The same group also used the organocatalytic Friedel−Crafts alkylation reaction of indoles for the construction of pyrroloindolines by a cascade−cyclization strategy for the synthesis of (−)-flustramine B.[24]

The MacMillan type catalyst has also been used for the enantioselective Friedel−Crafts alkylation of indoles with cyclic α,β-unsaturated aldehydes, leading to the synthesis of a serotonin reuptake inhibitor,[25] as well as reactions with α,β-enones.[26] In the former contribution, an enantioselectivity of 85% ee was obtained, while for the reaction of α,β-enones, only 28% ee was obtained. Furthermore, this catalyst type was also applied for an intramolecular indole alkylation reaction.[27]

Further improvements in the Friedel−Crafts alkylation with α,β-enones were shown to be feasible using catalytic salts, in which both an acid—an optically active amino acid derivative—and a base—a primary amine modified cinchona alkaloid—were applied.[28] This catalytic system gave high enantioselectivity, up to 96% ee, of the optically active Friedel−Crafts alkylation products when indoles were applied as the aromatic reaction partner. Primary amine-modified cinchona alkaloids, in combination with an achiral acid, were also demonstrated to catalyze the Friedel−Crafts alkylation of α,β-enones with indoles in up to 88% ee.[29]

Nitroalkenes are also suitable substrates for organocatalytic enantioselective Friedel−Crafts alkylation with indoles.[30] The best results in terms of enantioselectivity were obtained by Ricci et al.[30a] by using a simple chiral thiourea catalyst, which gave up to 89% ee for aromatic nitroalkenes and nearly similar results for an alkyl-substituted nitroalkene. For the latter reagent, however, a lower yield was obtained.

4. Alkylation with Carbonyl Compounds

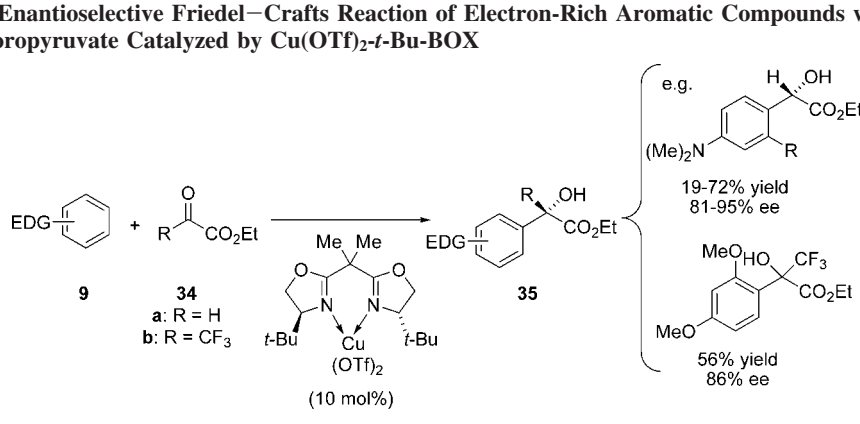
4.1. Copper Complexes

As in the case of alkene electrophiles, copper-based optically active catalysts have also played a key initial role in the development of asymmetric Friedel−Crafts addition to carbonyl electrophiles. Following the initial work from the groups of Casiraghi[3] and Erker,[4] Gathergood et al. reported in 2000 the use of $Cu(OTf)_2$-*t*-Bu-BOX to catalyze the addition of electron-rich benzene derivatives **9** and furans to ethyl glyoxylate **34a** and ethyl 3,3,3-trifluoropyruvate **34b** (Scheme 10).[31] In accordance with the accepted mode of binding of a 1,2-dicarbonyl compound to the chiral copper catalyst,[8] one face of the carbonyl compound is shielded by the *tert*-butyl substituent leading to the optically active arylmethyl alcohols **35** in good yield and generally with enantioselectivities >80% ee.

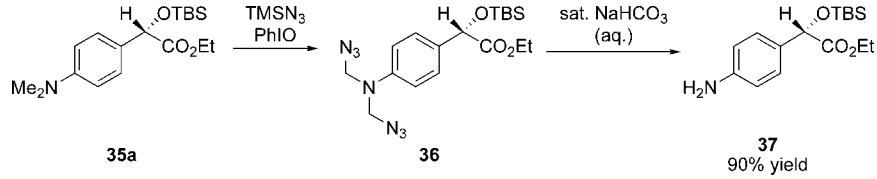
The optically active mandelic acid derivatives **35** obtained by the addition of substituted *N*,*N*-dimethylanilines to ethyl glyoxylate were demonstrated to undergo a synthetically useful demethylation reaction (Scheme 11). Using the TBS-protected *para*-dimethylamino mandelic acid ethyl ester **35a**, the bis-azide **36** was formed by reaction with iodosylbenzene and $TMSN_3$. Mild hydrolysis with aqueous $NaHCO_3$ liberated the free amine **37** in 90% yield. Along with a related deamination sequence,[22c] this transformation increased the synthetic potential of the Friedel−Crafts reaction with dialkylaniline derivatives.

As a continuation of the work shown in Scheme 10, the generality of ethyl 3,3,3-trifluoropyruvate **34b** as a carbonyl electrophile in asymmetric Friedel−Crafts alkylation reactions was demonstrated (Scheme 12).[32] Using the $Cu(OTf)_2$-*t*-Bu-BOX catalyst, different indoles were shown to be competent substrates delivering the products **38** in up to 94% ee. Pyrroles, as well as thiophenes and furans, also underwent

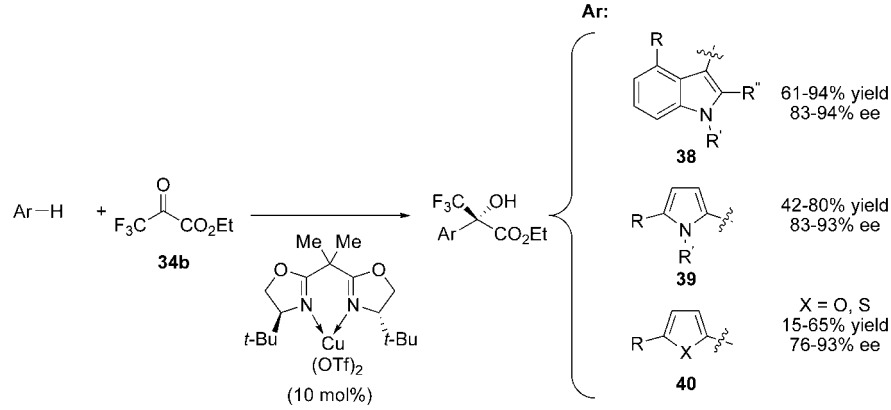
Scheme 10. Catalytic Enantioselective Friedel−Crafts Reaction of Electron-Rich Aromatic Compounds with Ethyl Glyoxlate and Ethyl 3,3,3-Trifluoropyruvate Catalyzed by $Cu(OTf)_2$-*t*-Bu-BOX



Scheme 11



Scheme 12. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles, Pyrroles, Furans, and Thiophenes with Ethyl 3,3,3-Trifluoropyruvate Catalyzed by Cu(OTf)$_2$-*t*-Bu-BOX



the Friedel−Crafts reaction with high levels of stereocontrol, providing enantioselectivities up to 93% ee of the optically active products **39** and **40**, respectively; however, in the case of the furans, reduced yields were observed.

In an interesting study from 2002, Corma et al. demonstrated the feasibility of employing solid-supported Cu(OTf)$_2$-Ph-BOX to catalyze the addition of 1,3-dimethoxybenzene to ethyl 3,3,3-trifluoropyruvate.[33] The catalyst was linked to a silica surface at the center portion of the ligand via a long methylene-sulfide linker (Figure 3). With the supported catalyst, up to 92% ee of the Friedel−Crafts-product was obtained, which does in fact exceed the selectivity observed under homogeneous conditions.

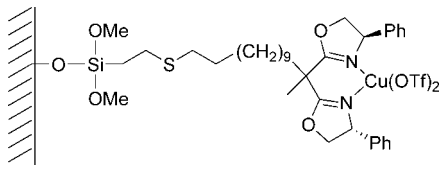


Figure 3. Solid-supported catalyst for the addition of 1,3-dimethoxybenzene to ethyl 3,3,3-trifluoropyruvate.

Additional use of ethyl 3,3,3-trifluoropyruvate **34b** in Cu(II)-catalyzed asymmetric Friedel−Crafts alkylations has been published recently. Lyle et al. have demonstrated the use of C_2-symmetric bipyridyl ligands in combination with Cu(OTf)$_2$ to effect the addition of various indoles to **34b** in good yields and with up to 90% ee.[34] Zhao et al. also contributed, by demonstrating the feasibility of performing the addition of aromatic ethers to **34b** under neat reaction conditions catalyzed by Cu(OTf)$_2$-diPh-BOX complexes.[35] By employing these conditions, simple aryl monoethers **9** undergo the asymmetric electrophilic addition in good to excellent yields and with excellent enantioselectivities (Scheme 13), thus complementing the use of synergistically activated aryl compounds such as 1,3-dimethoxybenzene as the nucleophilic reaction partner. The low amount of catalyst—1 mol %—used in this process is also noticeable.

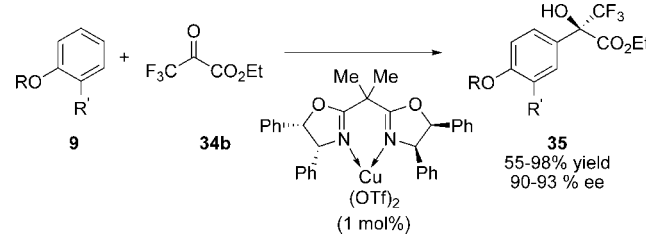
4.2. Other Metal Complexes

Alkoxide complexes of early transition metals are another class of hard Lewis acid catalysts, which have proven useful in asymmetric Friedel−Crafts alkylations with carbonyl electrophiles. In 2000, the group of Mikami demonstrated the use of Ti(O-*i*Pr)$_2$-(*R*)-6,6′-Br$_2$−BINOL to catalyze the addition of anisole **9c** and *n*-butyl phenyl ether **9d** to fluoral **41** (Scheme 14) affording synthetically interesting 1-aryl-2,2,2-trifluoro ethanol compounds **42**.[36]

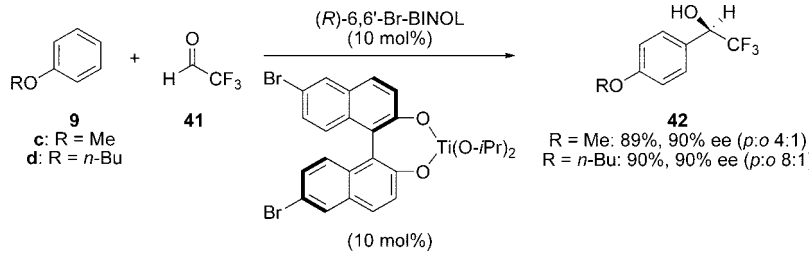
In the presence of the matched asymmetric activator[37] (*R*)-6,6′-Br$_2$-BINOL, the Friedel−Crafts products **42** were obtained in excellent yields and with up to 90% ee as a mixture (up to 8:1 selectivity) of *para*- and *ortho*-regioisomers. The preferential formation of the *para*-regioisomer rules out the involvement of a six-membered transition state assembly as suggested by Casiraghi for the *ortho*-selective addition of phenol to chloral mentioned above in "The Incubation Period".[3] Using the same catalyst, the group also reported the formation of Friedel−Crafts-like products in the reaction of fluoral with enol-silanes.[38]

These promising initial demonstrations of the potential of the Ti(IV)-BINOL complexes as carbonyl activators in asymmetric Friedel−Crafts alkylations warranted further advances being made using this catalyst system. Indeed, in 2004, Yuan et al. reported the use of Ti(O-*i*Pr)$_2$-6,6′-Br$_2$−BINOL to effect the highly enantioselective addition

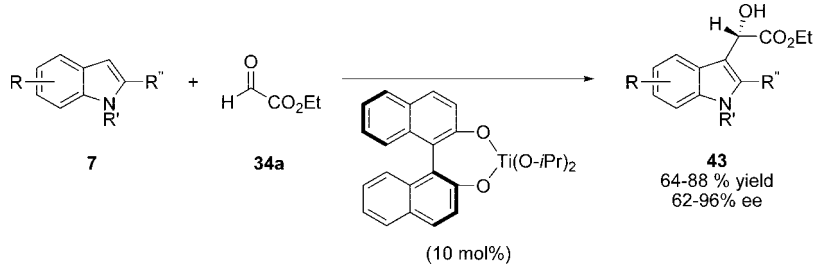
Scheme 13. Catalytic Enantioselective Friedel−Crafts Reaction of Electron-Rich Aromatic Compounds with Ethyl 3,3,3-Trifluoropyruvate Catalyzed by Cu(OTf)$_2$-diPh-BOX under Neat Conditions



Scheme 14. Catalytic Enantioselective Friedel−Crafts Reaction of Electron-Rich Aromatic Compounds with Fluoral Catalyzed by Ti(O-*i*Pr)$_2$-6,6′-(*R*)-Br$_2$-BINOL

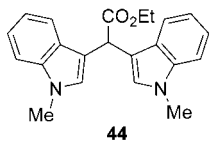


Scheme 15. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles with Ethyl Glyoxylate Catalyzed by Ti(O-*i*Pr)$_2$-BINOL

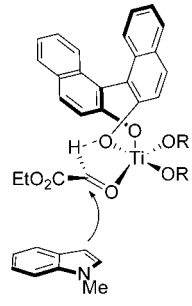


of aniline derivatives to ethyl glyoxylate (see Scheme 10).[39] Very recently, Dong et al. showed that indole derivatives **7** also could be engaged in a highly enantioselective Ti(IV)-BINOL-catalyzed Friedel−Crafts reaction with ethyl glyoxylate **34a**, leading to the optically active Friedel−Crafts adducts **43** in good to high yields and enantioselectivities (Scheme 15).[40] Various substitutions were tolerated in the indole nucleus, and it was observed that formation of bisindole products such as **44** was almost completely suppressed when the reactions were carried out in Et_2O at subzero temperatures.

The success of the transformation was found to be highly dependent on the carbonyl electrophile. Methyl 3,3,3-trifluoropyruvate was also shown to furnish the Friedel−Crafts product (see Scheme 12), but the reaction was scarcely selective, delivering the product in only 10% ee. This finding can be understood through the postulated model for the transition state (**45**),[39a,41] in which a formyl CH−O hydrogen bond plays an important role in stabilizing the transition state complex, as shown for the reaction of *N*-methylindole and ethyl glyoxylate. This stabilizing interaction is absent in the case of the trifluoropyruvate derivatives. Finally, other 1,2-dicarbonyl derivatives such as methyl pyruvate and *p*-chlorophenylglyoxal delivered only the corresponding bisindole products.



44



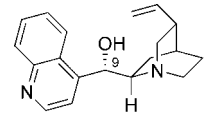
45

Aluminum and cobalt complexes have also been employed to facilitate Friedel−Crafts alkylations with carbonyl electrophiles. For instance, it was demonstrated that the use of a Al(III)-BINOL complex in stoichiometric amount can promote the addition of *N*,*N*-dimethylaniline to pyridinecarbaldehydes in an enantioselective manner with up to 50% ee,[42] and Kwiatkowski et al. have reported on the use of a Co(II)-(salen) catalyst for the addition of 2-methylfuran to ethyl glyoxylate under high-pressure conditions, giving the product in up to 76% ee.[43] Finally, the asymmetric carbonyl-Friedel−Crafts alkylation reaction has been employed as the last step of a two-step tandem oxa-Michael-Friedel−Crafts alkylation protocol leading to optically active chromanes in up to 81% ee. The best catalyst for this tandem sequence was found to be Mg(OTf)$_2$-1-Np-BOX.[44]

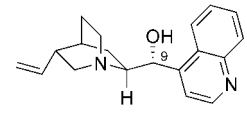
4.3. Organocatalysis

The activation of the carbonyl group through coordination to oxophilic Lewis acids has been the unifying principle in the metal-catalyzed Friedel−Crafts alkylation reactions discussed above. However, from the recent "organocatalysis revolution", another principle has emerged, which is just starting to unravel its potential—namely, the use of chiral Brønsted acid catalysts for electrophilic activation of unsaturated polarized molecular entities including the carbonyl group. As carbonyl compounds do not undergo appreciable protonation by Brønsted acids of medium strength, the examples of Brønsted acid catalysts for asymmetric carbonyl-Friedel−Crafts alkylations mentioned here do often incorporate another coordinating functionality—such as amines—which probably assists in the positioning of the reactants in the transition state through hydrogen-bonding interactions.

In 2005, Török et al. reported the use of simple cinchona alkaloids, such as cinchonine and cinchonidine, in the enantioselective addition of indoles to ethyl 3,3,3-trifluoropyruvate **34b** (See Scheme 12 for the reaction).[45]

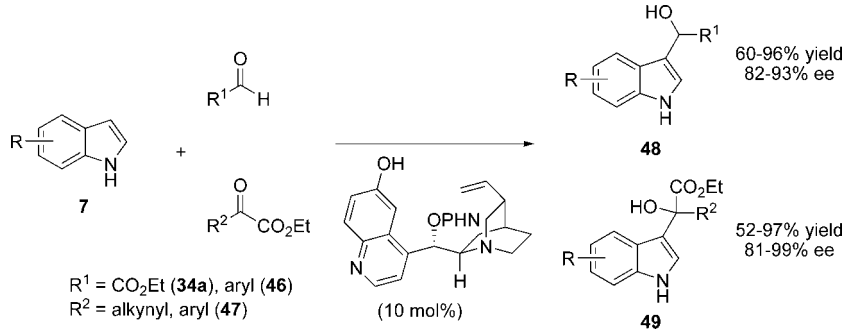


cinchonine



cinchonidine

Scheme 16. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles with Carbonyl Compounds Catalyzed by a Cinchona−Alkaloid Derivative; PHN = Phenanthrene



For a large number of substrates (18 examples reported), the Friedel−Crafts products were obtained in excellent yields and with enantioselectivities >80% ee. Partly based on kinetic measurements, the authors documented three prerequisites for obtaining high selectivity in this reaction. A free hydroxyl group at C9 of the cinchona alkaloid catalyst, an unblocked (i.e., coordinating) quinuclidine nitrogen atom, and finally that the indole should not be *N*-alkylated (*N*-methylindole provided racemic products). These, and additional structural observations, prompted the authors to suggest a transition state assembly being organized by hydrogen-bonding interactions, but a detailed model was not suggested.

Two additional reports of chiral Brønsted acid-catalyzed addition of indoles to carbonyl electrophiles have emerged. Using a bis-triflamide catalyst derived from optically active 1,2-diphenylethylenediamine, up to 63% ee in the reaction between different indoles and ethyl glyoxylate was obtained.[46] Lastly, in an impressive study from 2006, the Deng group reported another example of the use of cinchona alkaloids as catalysts for the asymmetric carbonyl-Friedel−Crafts reaction.[47]

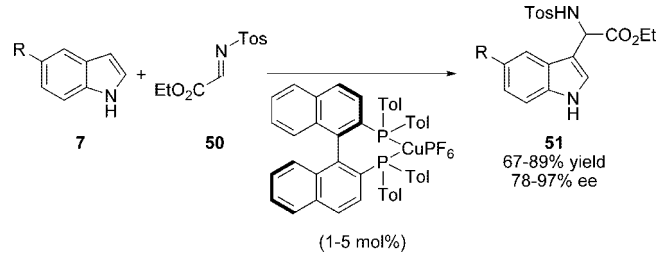
As shown in Scheme 16, the quinidine (or quasienantiomer quinine)-derived catalyst developed in the Deng group accomplishes the addition of various indoles **7** to a diverse array of carbonyl electrophiles. Most impressively, also, simple aromatic aldehydes **46** could be converted into the corresponding Friedel−Crafts products **48**, and in all cases, synthetically useful selectivities and yields were observed. Although the mode of activation in this case also presumably involves a number of relatively weak hydrogen-bonding interactions, the robustness of the system is underscored by the demonstration that for some of the slower reacting substrates, the reactions could be performed at 10 M concentration of the reactants and even at 70 °C. Under these forcing conditions, enantioselectivities exceeding 90% ee were still observed.

5. Alkylation with Imines

5.1. Copper Complexes

The first example of a copper-catalyzed aza-Friedel−Crafts reaction was reported by Johannsen in 1999 (Scheme 17).[6] In the presence of the $CuPF_6$-Tol-BINAP[48] complex, it was shown that different indoles **7** underwent a highly enantioselective addition to tosyl-protected α-iminoester **50** resulting in the production of optically active indole α-amino acid derivatives **51**. The optimal conditions identified involved performing the reactions at −78 °C in THF, and in many of the examples reported, one recrystallization of the product was sufficient to obtain enantiopure material. Also, the application of pyrroles **18** in this reaction was tested. Although pyrrole itself gave the *N*-addition product, both *N*-methylpyrrole and 2-acetylpyrrole afforded the corresponding optically active pyrrolo α-amino esters in up to 84 and 94% ee, respectively.

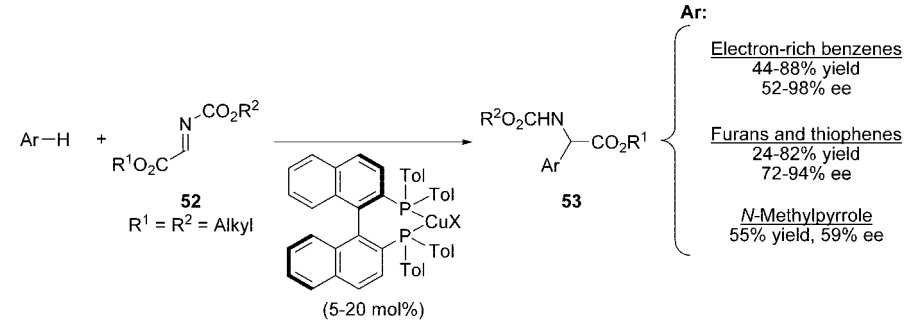
Scheme 17. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles with a Tos-Protected α-Iminoester Catalyzed by $CuPF_6$-Tol-BINAP

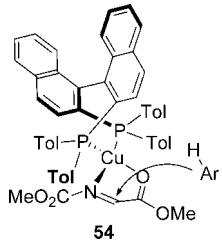


This paper was soon hereafter followed by two other papers also describing the copper-catalyzed asymmetric aza-Friedel−Crafts reaction. It was demonstrated that the use of carbamate-protected α-iminoesters **52** as the electrophilic reaction component in the enantioselective Friedel−Crafts reaction with a variety of electron-rich aryl- and heteroaryl compounds gave the corresponding optically active aromatic and heteroaromatic α-amino acid derivatives in moderate to good yields and high enantiomeric excesses (Scheme 18).[49] Although the carbamate-protected α-iminoesters **52** are slightly less stable than the corresponding tosyl-protected electrophiles **50**, the more convenient strategies available for carbamate deprotection following the catalytic reaction give this protocol an advantage from a synthetic perspective.

As shown in Scheme 18, various aryl nucleophiles can be employed in this reaction resulting in the α-aryl α-aminoesters **53** being obtained in good yields and good to excellent enantioselectivities. On the basis of the absolute stereochemistry induced by the catalyst and DFT level calculations, a model (**54**) in accordance with the observed stereoinduction was suggested for the coordination of the α-iminoesters **52** to the chiral catalyst and the approach of the aromatic compound. The α-iminoester coordinates the copper center through the imine-nitrogen atom and the ester carbonyl-oxygen atom, and in this intermediate, one of the tolyl groups (bold) efficiently screens the *Si* face of the imine, allowing nucleophiles to only approach from the opposite side.

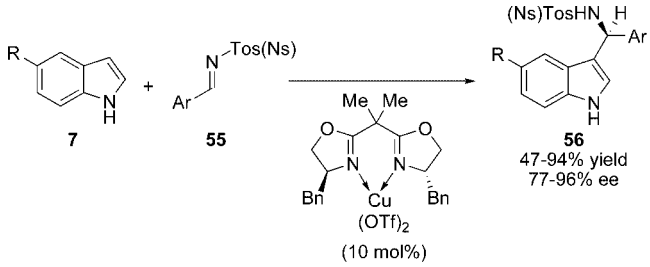
Scheme 18. Catalytic Enantioselective Friedel−Crafts Reaction of Aromatic Compounds with Carbamate-Protected α-Iminoesters Catalyzed by CuX-Tol-BINAP





The most recent example of the use of optically active copper-based catalyst for the aza-Friedel−Crafts alkylation was reported by Jia et al. in 2006 (Scheme 19).[50] In this study, the authors demonstrated the use of $Cu(OTf)_2$-Bn-BOX as a highly efficient catalyst for the addition of indoles **7** to aromatic *N*-sulfonyl aldimines **55**, thus expanding the imine-electrophiles applicable to the copper-catalyzed aza-Friedel−Crafts reaction beyond the above-mentioned α-iminoesters.

Scheme 19. Catalytic Enantioselective Friedel−Crafts Reaction of Indoles with Aromatic Sulfonyl Aldimines Catalyzed by $Cu(OTf)_2$-Bn-BOX



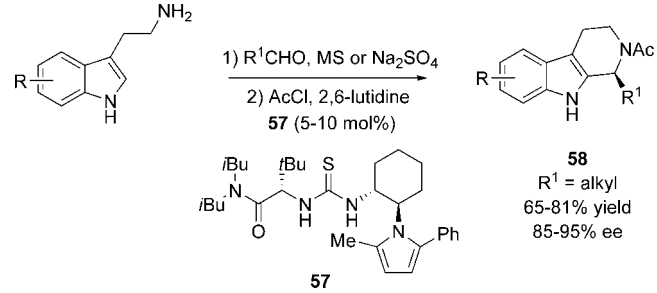
A collection of aromatic aldimines **55** with either tosyl or nosyl as the protecting group was shown to deliver the 3-indolylarylmethamine derivatives **56** in medium to excellent yield and up to 96% ee. The presence of the sulfonyl-activating group proved critical to the success of the transformation; for instance, when employing the corresponding *N*-phenyl aldimine, the Friedel−Crafts product was obtained as a racemic mixture in 65% yield.

5.2. Organocatalysis

As in the case of organocatalytic carbonyl-Friedel−Crafts reactions, an increasing number of reports describing the use of chiral Brønsted acids in asymmetric aza-Friedel−Crafts reaction have appeared recently. Curiously, of the existing papers describing organocatalytic aza-Fridel-Crafts reactions, only two different types of Brønsted acids are employed as follows: optically active thiourea derivatives and phosphoric acid catalysts derived from BINOL.

The first report to appear was by Taylor and Jacobsen in 2004, who employed a truncated version **57** of a thiourea catalyst developed for the asymmetric Strecker reaction[51] to effect the enantioselective intramolecular cyclization of indoles to in situ-generated *N*-acyliminium ions (Scheme 20)—the acyl−Pictet−Spengler reaction.[52] The optically active tetrahydro-β-carboline derivatives **58** resulting from this process are important intermediates for indole alkaloid synthesis.

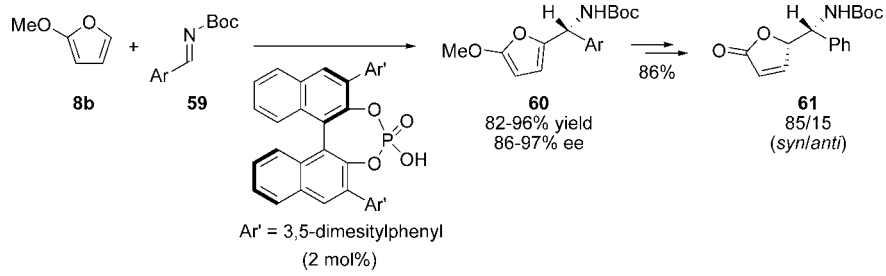
Scheme 20. Catalytic Enantioselective Acyl−Pictet−Spengler Reaction Producing Tetrahydro-β-carboline Derivatives Catalyzed by a Thiourea Organocatalyst



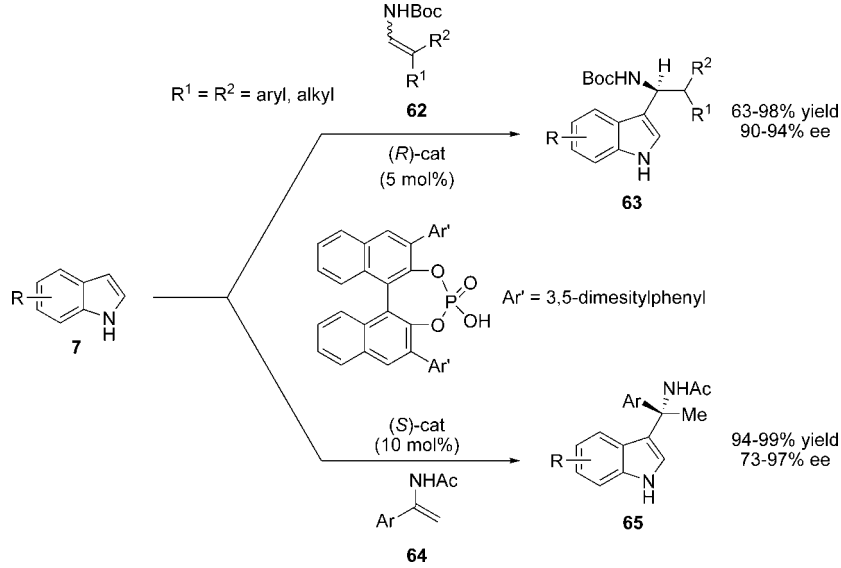
At the time of writing, two other reports on organocatalytic enantioselective Pictet−Spengler cyclizations leading to optically active tetrahydro-β-carbolines have occurred—both employing optically active phosphoric acid catalysts. List et al. described the first enantioselective Pictet−Spengler reaction,[53] and Hiemstra et al. recently demonstrated the use of sulfenyliminium ions in a transformation related to the acyl−Pictet−Spengler reaction mentioned above.[54]

The first report describing an intermolecular organocatalytic aza-Friedel−Crafts reaction appeared in 2004. Employing optically active BINOL-derived phosphoric acid catalyst, Uraguchi et al. demonstrated the addition of 2-methoxyfuran **8b** to different aromatic and heteroaromatic *N*-Boc aldimines **59**, affording the Friedel−Crafts products **60** in excellent

Scheme 21. Catalytic Enantioselective Addition of 2-Methoxyfuran to *N*-Boc Aldimines Catalyzed by a Phosphoric Acid Catalyst



Scheme 22. Catalytic Enantioselective Addition of Indoles to Enecarbamates and Enamides Catalyzed by a Phosphoric Acid Catalyst



yields and enantioselectivities (Scheme 21).[55] The practicality of the process was demonstrated by conducting the reaction on a gram-scale in the presence of only 0.5 mol % of the catalyst. Furthermore, it was demonstrated (in the case of Ar = Ph) that the furan ring could be readily converted into the corresponding γ-butenolide **61** in 86% yield favoring the *syn*-diastereomer.

This initial report has spurred an enormous interest in developing intermolecular Brønsted acid-catalyzed aza-Friedel−Crafts reactions; two recent papers report the enantioselective addition of indoles to sulfonyl imines. Wang et al. employed a thiourea-functionalized cinchona alkaloid catalyst to achieve this transformation for both alkyl- and arylimines in excellent yields and selectivities,[56] and Kang et al. achieved an equivalent transformation through the use of a phosphoric acid catalyst.[57] Also, benzoyl groups have been used as the imine-activating groups in phosphoric acid-catalyzed aza-Friedel−Crafts reactions. In two recent papers, the group of Antilla described the addition of *N*-alkyl indoles[58a] and *N*-alkyl pyrroles,[58b] respectively, to aromatic *N*-benzoyl aldimines. Both reactions took place in good yields and with excellent stereoselectivities.

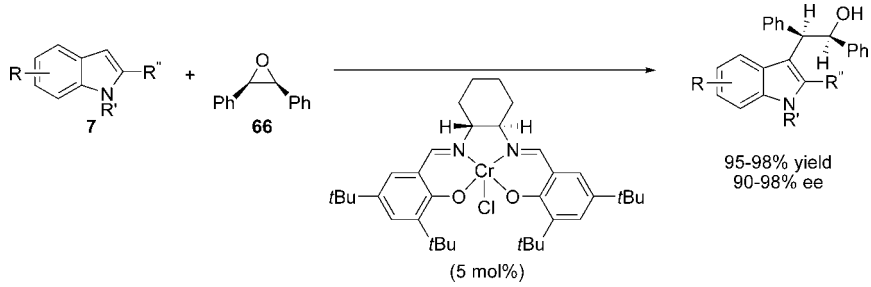
One drawback to the use of carbonyl-protected imines in aza-Friedel−Crafts reactions is their somewhat limited stability. This is especially pronounced in the case of aliphatic imines that are readily converted into the corresponding enecarbamates or enamides. However, these compounds were shown in two independent contributions to be viable imine precursors when they are in the presence of a phosphoric acid catalyst (Scheme 22). Terada et al. demonstrated that Boc-protected enecarbamates **62** could be reacted with substituted indoles **7** to give the Friedel−Crafts products **63** in excellent yields and selectivities (Scheme 22, top).[59] (*Z*)- and (*E*)-Enecarbamates were shown to afford the products in identical selectivities but with different rates—a finding that was advocated by the authors to indicate rate-determining formation of a common imine intermediate by protonation of the enecarbamates by the phosphoric acid catalyst. Also, the formation of quaternary stereocenters is possible through this methodology as demonstrated by Jia et al. (Scheme 22, bottom).[60] In this study, α-aryl enamides **64** were employed as the imine precursors, and the Friedel−Crafts products **65** were obtained with excellent selectivities. The importance of both the indole NH and the enamide NH for the success of this transformation was clearly demonstrated as methylation of either position lead to complete loss of reactivity.

6. Miscellaneous

The last two types of reactions to be discussed in relation to the catalytic enantioselective Friedel−Crafts reaction are epoxide openings and allylic alkylations with aromatic nucleophiles.

Activating epoxides toward opening by nucleophiles by coordination to chiral Lewis acid catalysts is a strategy that has been employed for a number of different heteroatom and carbon nucleophiles. In 2004, Bandini et al. succeeded in the opening of a number of 1,2-disubstitued epoxides by indole derivatives in the presence of optically active Cr(III)Cl-(salen) complexes.[61] In the case of racemic ep-

Scheme 23. Catalytic Enantioselective Opening of *meso*-Stilbeneoxide with Indoles Catalyzed by a Cr(III)Cl−(Salen) Complex



oxides, an efficient kinetic resolution was observed with *s* values ranging from 10 to 30. Furthermore, the same complex was also an efficient catalyst for the enantioselective opening of *meso*-stilbeneoxide **66** with different indoles **7** as shown in Scheme 23.

The same group also reported an intramolecular enantioselective palladium-catalyzed allylic alkylation of indoles with allyl carbonates.[62] As mentioned in the Introduction, the use of optically active coinage metal complexes to accomplish these types of Friedel−Crafts alkylation reactions has so far not been reported.

7. Conclusion and Perspectives

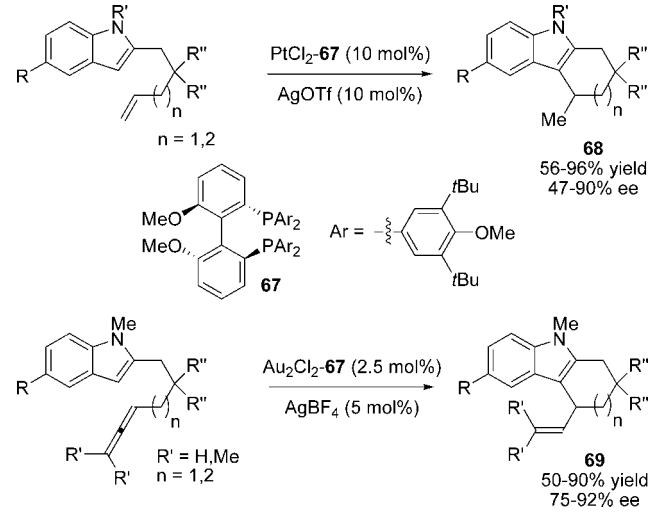
Chiral copper complexes have played a special role in the development for catalytic enantioselective Friedel−Crafts alkylation reactions. For the three main classes of electrophiles employed in these reactions, copper-based catalysts are able to deliver the Friedel−Crafts adducts in high yields and with excellent stereocontrol. The introduction of organocatalytic methodologies in complement to the metal-catalyzed processes has made the catalyst arsenal even more diverse and powerful. However, there are still important undeveloped areas in relation to the enantioselective Friedel−Crafts alkylation reaction.

For instance, the types of nucleophiles that are able to participate in enantioselective Friedel−Crafts reactions have remained "essentially constant" since the first publications. Broadly speaking, the enantioselective Friedel−Crafts reaction works well within the categories discussed in this review but only for electron-rich aromatic and heteroaromatic compounds. An important task would be to develop catalytic systems able to effect these Friedel−Crafts alkylation reactions also for simple benzene derivatives. Systems relying on multiple activation or systems taking place at high reaction temperatures could be possible routes toward this goal.

Simple unsaturated organic compounds such as alkenes or allenes could have enormous potential as prochiral alkylating agents in asymmetric Friedel−Crafts alkylation reactions. Arguably, the activation of such compounds is very challenging when compared to the electrophiles discussed until now in this review; however, the first steps toward this objective have recently been taken, and interestingly, they may portend a new major role for coinage metals in the asymmetric Friedel−Crafts alkylation reaction. In two papers, Widenhoefer et al. have demonstrated the enantioselective intramolecular addition of indoles to unactivated alkenes[63] and allenes[64] (Scheme 24).

In the former case, a cationic platinum complex $PtCl_2$-**67**-AgOTf enables the cyclization to **68** in good to excellent yields and up to 90% ee, and in the latter case, a cationic gold complex Au_2Cl_2-**67**-2$AgBF_4$ results in the formation of **69** in up to 92% ee. Although a mechanism involving

Scheme 24. Catalytic Enantioselective Intramolecular Addition of Indoles to Unactivated Alkenes and Allenes Catalyzed by Cationic Coinage Metal Complexes



indole C−H activation followed by alkene migratory insertion and finally protonolysis can be envisioned, the authors have provided evidence (albeit in relation to an equivalent non asymmetric process)[65] supporting a mechanism in which the key bond formation results from the attack of the indole onto a metal-coordinated alkene followed by protonolysis, thus making the process a catalytic Friedel−Crafts alkylation reaction.

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9. Note Added in Proof

Since the submission of this review, papers have appeared as follows: Jacobsen et al. have described the application of a chiral thiourea organocatalyst for the enantioselective Pictet−Spengler type cyclization of hydroxylactams.[66a] Chan et al. have demonstrated the use of a chiral ferrocenyl P/S ligand palladium complex for the enantioselective allylic alkylation of indoles.[66b]

10. References

(1) (a) For a historical introduction to Friedel and Crafts, see for example, Olah, G. A.; Dear, R. E. A. In *Friedel−Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley and Sons: New York, 1963, p 1. (b) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley and Sons: New York, 1973.
(2) See for example,
(a) For recent reviews on the Friedel−Crafts reaction, see, for example,

Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A.; *Synlett.* **2005**, 1199. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (c) Jørgensen, K. A. *Synthesis* **2003**, 1117. (d) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (e) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; p 1313. (f) Olah, G. A.; Khrisnamurti, R.; Prakesh, G. K. S. In *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. III, p 293. (g) Heaney, H. In *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. II, p 733. (h) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry: A Century of Discovery*; Wiley-Interscience: New York, 1984.

(3) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Fava, G. G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.

(4) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem., Int. Ed.* **1990**, *29*, 512.

(5) (a) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249. (b) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348.

(6) Johannsen, M. *Chem. Commun.* **1999**, 2233.

(7) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

(8) (a) For a review of the use of chiral bisoxazoline−Lewis acid complexes in asymmetric synthesis, see: (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(9) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347.

(10) (a) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (b) Zhou, J.; Ye, M.-C.; Huang, Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309. (c) Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432. (d) Ye, M.-C.; Li, B.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6108.

(11) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099.

(12) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2005**, *70*, 739.

(13) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154.

(14) Singh, P. K.; Bisai, A.; Singh, V. K. *Tetrahederon Lett.* **2006**, *48*, 1127.

(15) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281.

(16) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (c) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029.

(17) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Helv. Chem. Acta* **2003**, *86*, 3753.

(18) (a) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843. (b) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigare, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511. (c) Bandini, M.; Garelli, A.; Rovinetti, M.; Tommasi, S.; Umani-Ronchi, A. *Chirality* **2005**, *17*, 522.

(19) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601.

(20) (a) Angeli, M.; Bandini, M.; Garelli, A.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Org. Biomol. Chem.* **2006**, *4*, 3291. See also (b) Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157.

(21) (a) Jia, Y.-X.; Zhu, S.-F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 75. (b) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115. (c) Liu, H.; Xu, J.; Du, D. M. *Org. Lett.* **2007**, *9*, 4725.

(22) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

(23) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.

(24) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482.

(25) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437.

(26) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799.

(27) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847.

(28) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaoli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403.

(29) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816.

(30) (a) Herrera, R. P.; Sqarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (b) Flemming, E. E.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (c) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566. Organocatalytic alkylation of 2-naphthols with nitroalkenes: (d) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228.

(31) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

(32) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009.

(33) Corma, A.; García, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.* **2002**, 1058.

(34) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901.

(35) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127.

(36) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597.

(37) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613.

(38) Ishii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, *1*, 2013.

(39) (a) Yuan, Y.; Wang, X.; Li, X.; Ding, K. *J. Org. Chem.* **2004**, *69*, 146. For the use of a chiral calixarene-like salen-Ti(O-*i*Pr)$_4$ complex as a catalyst for the same transformation, see (b) Zhu, C.; Yuan, C.; Lv, Y. *Synlett* **2006**, 1221.

(40) Dong, H.-M.; Lu, H.-H.; Lu, L.-Q.; Chen, C.-B.; Xiao, W.-J. *Adv. Synth. Catal.* **2007**, *349*, 1597.

(41) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513.

(42) Gothelf, A. S.; Hansen, T.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 854.

(43) Kwiatkowski, P.; Wojaczyñska, E.; Jurczak, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3643.

(44) Van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953.

(45) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakesh, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086.

(46) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284.

(47) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063.

(48) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.

(49) (a) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (b) Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352.

(50) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621.

(51) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

(52) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(53) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.

(54) Wanner, M. J.; van der Hass, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485.

(55) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. See also (b) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Cat.* **2007**, *349*, 1863.

(56) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.

(57) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.

(58) (a) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (b) Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065.

(59) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.

(60) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565.

(61) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 84.

(62) (a) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424. See also (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.

(63) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801.

(64) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935.

(65) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700.

(66) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T. L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295.

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