

FRIEDEL-CRAFT REACTION: A REVIEW

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ABSTRACT

Friedel–Crafts reaction is one of the oldest carbon–carbon bond forming processes, and is still an attractive method to introduce substituents on aromatic rings. This article mainly focused on Friedel–Crafts acylation, arylation, alkylation especially given by electron-rich arenes forming reaction in organic synthesis in presence of different catalysts.

Key words: Friedel-craft acylation, Friedel-craft alkylation, Friedel-craft arylation.

INTRODUCTION

Friedel–Crafts alkylation is one of important and convenient reactions used in the preparation of alkyl substituted arenes. Generally, alkyl halide, alkyl sulfonate, alkene, alcohol, and alkene oxide were used as alkylation reagents in the Friedel–Crafts alkylation. However, several examples of the Friedel–Crafts alkylation of arenes with ketones and N-arylsulfonyl aldimines as alkylation reagents were observed. In a few cases, aromatic aldehydes were also found to be used in the Friedel–Crafts alkylation, especially for electron-rich arenes and aromatic heterocyclic compounds, such as phenols, indoles, pyrroles, and furans and thiophenes, etc. It has been well-known that formaldehyde could undergo a Friedel–Crafts reaction with benzene to yield benzyl chloride in the presence of anhydrous zinc chloride and hydrogen chloride via benzyl alcohol as an intermediate, called chloromethylation reaction. It is also known that the reaction of benzaldehyde and

benzene produced diphenylmethanol, which could further yield triphenylmethane under the catalysis of anhydrous aluminum chloride¹.

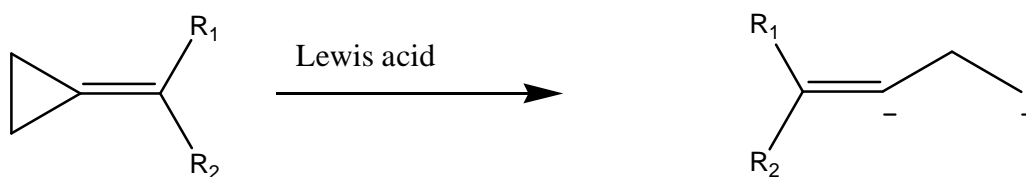
Friedel–Crafts reaction is one of the oldest carbon–carbon bond forming processes, and is still an attractive method to introduce substituents on aromatic rings. Initial works concerned Friedel–Crafts acylation from acyl chlorides or alkylation from alkyl halides. To perform acylations, Lewis acids are needed. More than stoichiometric amounts of AlCl₃ or BF₃ are required whereas catalytic amounts of rare-earth triflates, more specially scandium triflate, perfluorinated rare earth metals, gallium triflate or bismuth triflate, allow the formation of the expected products.³

The Friedel–Crafts reactions represent a powerful tool to introduce new carbon–carbon bond in aromatic compounds.¹ This reactions can be used for a method to build up polycyclic structure as well. The application of α -amido sulfones has been

utilized through the formation of N-acyl iminium ions on treatment with Lewis acid.⁴ Methylalumoxane (MAO) has been used as the important cocatalyst of alkene polymerization catalyzed by metallocenes and post-metallocene transition metal complexes since its discovery by Kaminsky. MAOs, having the general formula $[-Al(Me)-O-]_n$ and high molecular weights, abstract the alkyl or halogeno ligand of the transition metal (Ti, Zn, etc.) catalysts and form cationic alkyl complexes, which are regarded as the active species of the alkene polymerization. The bulky anion, formed from the above reaction of MAO with the halogeno ligand, does not coordinate the cationic transition metal firmly and enhances coordination of the monomer to the metal center. Thus, high Lewis acidity and bulky structure of MAO serve to convert the neutral transition metal complexes to the cationic catalytically active species. Lewis acidic MAO initiates the cationic polymerization of isobutene and methacrylates and copolymerization of 1,3-butadiene with methacrylates. Coordination of the ester group of methacrylates to Lewis acidic Al center of MAO is important for promoting the smooth polymerization.⁷

Organocatalysts have exhibited immense promise in the synthesis of multicomponent reactions. The catalytic property of small organic molecules like cinchona alkaloids and amino acids are well known. However much attention has been focused on L-proline, an inexpensive, and efficient catalyst. L-Proline has been found to be very effective in enamine-based direct catalytic asymmetric aldol, Mannich, Diels–Alder, and Knoevenagel type of reactions.¹⁴

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis. MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. Three general reaction pathways for MCPs have been disclosed for reactions promoted by transition metals such as Pd, Rh, Ru, and Pt. Recently, we found that the ring-opening reactions of MCPs with alcohols and other nucleophiles catalyzed by Lewis acids $[Ln(OTf)_n]$ ($Ln=Sn, Yb, Sc$) took place via a novel pathway to give the corresponding ring-opened products under mild conditions.¹²

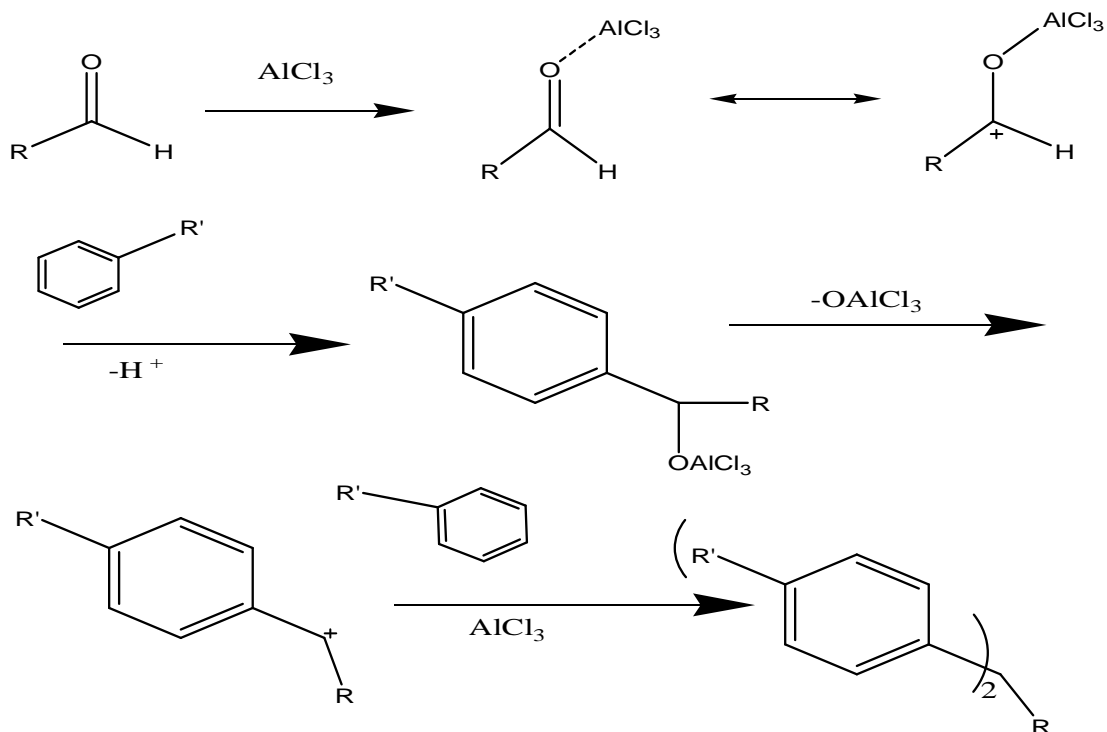


The reaction pattern of MCPs in the presence of Lewis acid.

1. Solvent-free, AlCl₃-promoted tandem Friedel–Crafts reaction of arenes and aldehyde.

Tandem Friedel–Crafts reaction of arenes and aldehydes under the catalysis of Lewis acid was investigated. Both aromatic and aliphatic

aldehydes underwent a tandem Friedel–Crafts alkylation with electron-rich arenes to afford 1, 1, 1-triaryl/1, 1-diaryllkanes in the presence of anhydrous aluminum chloride under solvent-free conditions.¹

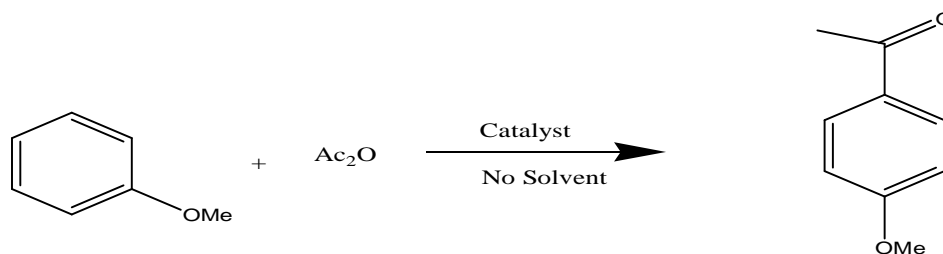


Mechanism of Friedel-Craft alkylation of arene and aldehyde

2. Friedel-Craft Reaction is catalysed by perfluorinated rare earth metal.

The Friedel-Craft reaction of anisole with acetic anhydride can be carried out in the presence of perfluorinated rare earth metal catalyst without organic solvent. Perfluorodecalin ($C_{10}F_{18}$, cis and trans mixture) can be used as a fluoruous

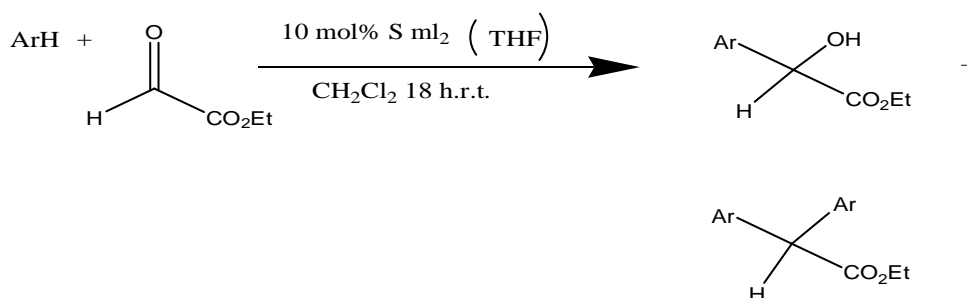
phase solvent for this reaction. Whereas the reaction of *N,N*-dimethylaniline with acetic anhydride did not give the corresponding Friedel-Craft reaction product. The Friedel-Craft reaction of *N,N*-dimethylaniline with ethyl glyoxylate was also examined in the presence of perfluorinated Lewis acid.²



3. Friedel-Crafts reactions catalyzed by samarium diiodide.

Samarium diiodide is an efficient precatalyst for the Friedel-Crafts reaction involving various aromatic substrates and chelating electrophiles. Alkyl 3,3,3-trifluoropyruvates are transformed into α -hydroxyesters in good

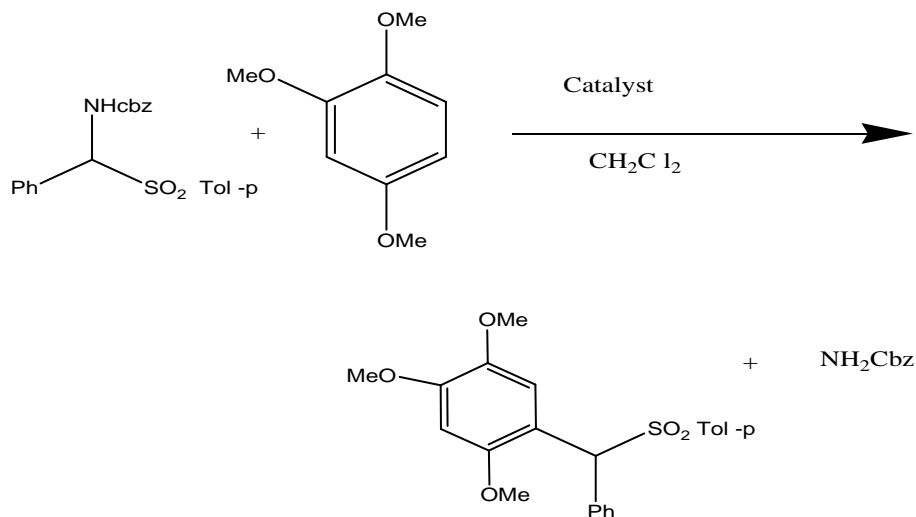
yields with total regioselectivity. In reactions involving an ethyl glyoxylate or a glyoxylic imine, α -hydroxyesters or α -aminoesters are obtained with variable amounts of products resulting from a double Friedel-Crafts reaction.³



4. Amberlyst-15: an efficient and reusable catalyst for the Friedel-Crafts reactions of activated arenes and heteroarenes with α -amido sulfones.

The heterogeneous Amberlyst-15 catalyst displays efficient catalytic properties for the Friedel-Crafts reactions between an activated arenes or heteroarenes and α -amido sulfones.

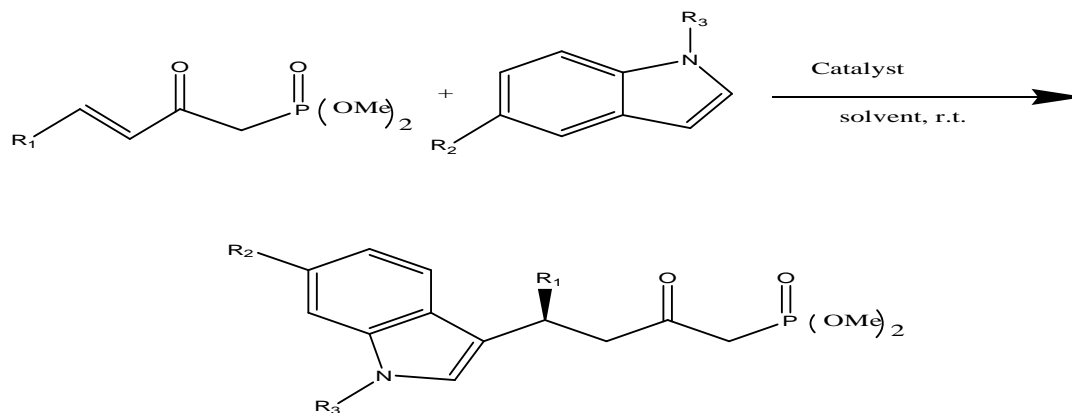
Various α -amido sulfones on treatment with 1, 2, 4-trimethoxy benzene give the Friedel-Crafts reaction products in very good yield. The reactions with heteroarenes show moderate yield of the product. The catalyst can be easily recycled without significant loss of activity.⁴



5. Chiral Pd-catalyzed enantioselective Friedel-Crafts reaction of indoles with γ,δ -unsaturated β -keto phosphonates.

The catalytic enantioselective Friedel-Crafts alkylation reaction promoted by chiral palladium complexes is described. The

treatment of indoles with γ,δ -unsaturated β -keto phosphonates under the mild reaction conditions afforded the corresponding Friedel-Crafts alkylation adducts with excellent enantioselectivities (up to 99%).⁵

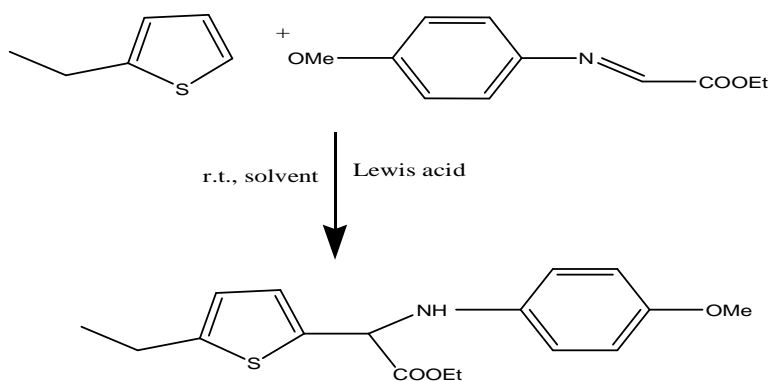


Friedel –Craft reaction of indoles with γ,δ -unsaturated β keto phosphonates.

6. The study of Friedel-Crafts alkylation reaction of thiophenes with glyoxylate imine catalyzed by Fe (III): an easy access to α -aminoesters.

A Friedel-Crafts alkylation reaction of thiophenes with glyoxylate imine was

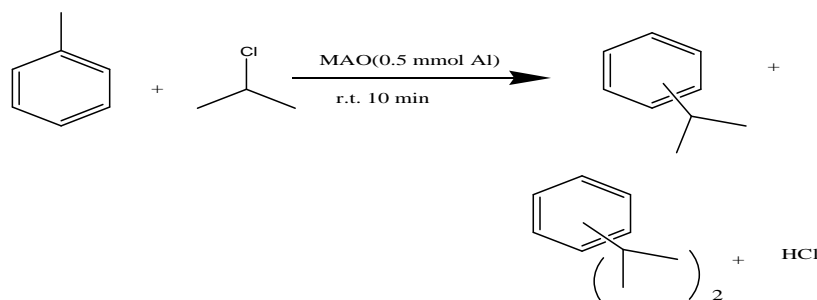
developed to give α -aminoesters. In the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as the catalyst, various α -aminoesters were prepared with moderate to high yields (up to 95%) except for some special substrates.⁶



7. MAO-catalyzed Friedel–Crafts reactions of toluene with chloroalkanes and with propylene.

The reaction of 2-chloropropane with toluene in the presence of methylalumoxane (MAO) produces a mixture of mono-, and diisopropyltoluenes. Catalytic activity of MAO in this reaction is similar to that of AlCl_3 . 1-

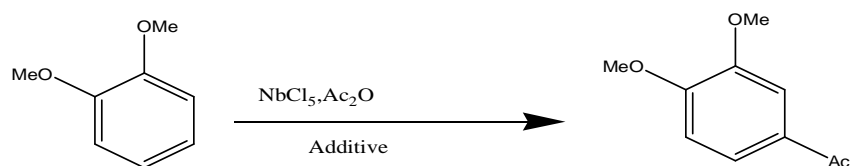
Chlorobutane and CH_2Cl_2 react with toluene to afford a mixture of n-butyltoluene, sec-butyltoluene and bistolylmethane. The reaction is preceded by an induction period. MAO catalyzes the Friedel–Crafts reaction of propylene with toluene in the presence of added chloroalkane to form a mixture of mono-, di-, and triisopropyltoluenes.⁷



8. Niobium pentachloride-silver perchlorate as an efficient catalyst in the Friedel-Crafts acylation and Sakurai-Hosomi reaction of acetals.

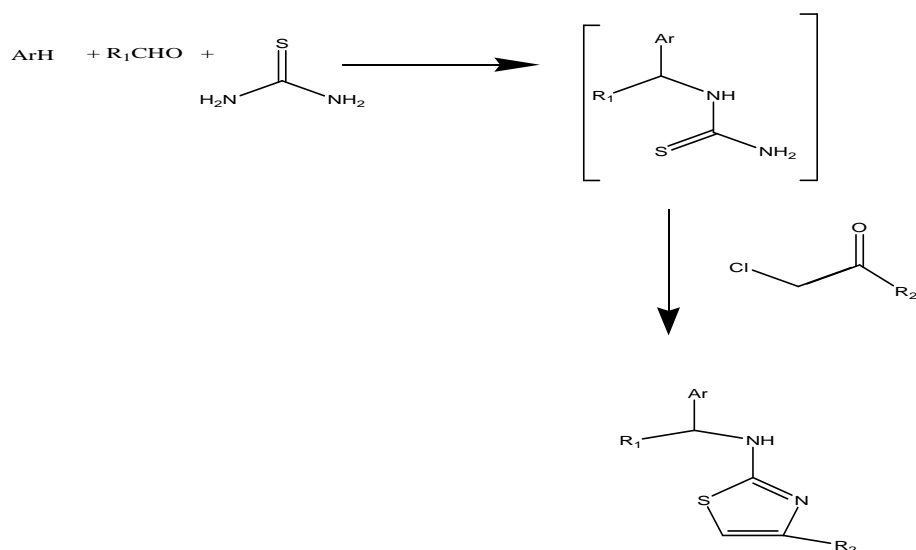
Friedel-Crafts acylation catalyzed by niobium pentachloride with silver salt is described. Aromatic compounds with Ac₂O or Bz₂O

were smoothly converted into the corresponding ketones in good to excellent yields. This system was also applied to the Sakurai-Hosomi reaction using acetals. The reaction proceeded quite rapidly to give the desired products in excellent yields.⁸



9. A tandem Aza-Friedel-Crafts reaction/Hantzsch cyclization: a simple procedure to access polysubstituted 2-Amino-1,3-thiazoles. A tandem Aza-Friedel-Crafts reaction / Hantzsch cyclization is described to access

various polysubstituted 2-amino-1,3-thiazoles from electron-rich (hetero)-aromatic rings, aldehydes, thiourea and α -chloroketones.⁹



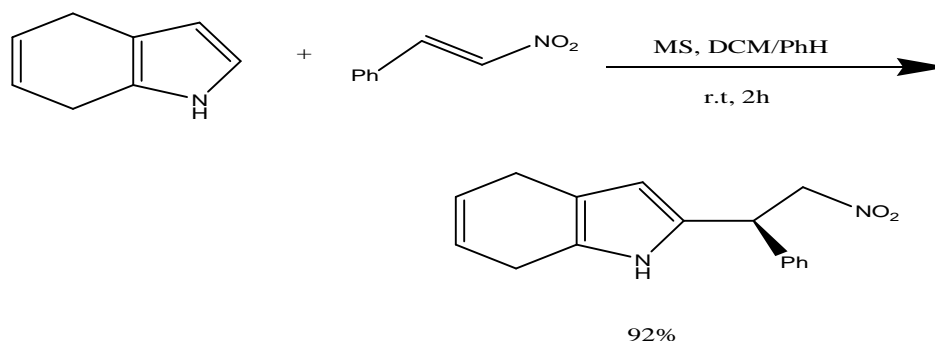
The synthesis of polysubstituted 2-amino 1, 3-thiazoles

10. A theoretical investigation into chiral phosphoric acid-catalyzed asymmetric Friedel-Crafts reactions of nitroolefins and 4,7-dihydroindoles: reactivity and Enantioselectivity.

This article mainly focused on high level Density Functional Theory (DFT) studies on the chiral phosphoric acid-catalyzed Friedel-Crafts reactions between 4,7-dihydroindoles and nitroolefins. Firstly, the reactivities of 4,7-dihydroindole and indole in the chiral phosphoric acid-catalyzed Friedel-Crafts reactions with nitroolefin have been compared. The higher reactivity of 4,7-dihydroindole could be attributed to its

higher HOMO energy as well as its more suitable trajectory to attack the nitroolefin in the transition state. Secondly, the origin of the enantioselectivity of the chiral phosphoric acid-catalyzed Friedel-Crafts reaction of 4,7-dihydroindole with nitroolefin has been studied using complete models on PBE1PBE/[6-311pG(d,p), 6-31G(d,p)] level. When (S)-1b was used as the catalyst, the enantioselectivity of the reaction is entirely controlled by the steric effect between the catalyst and the substrate.

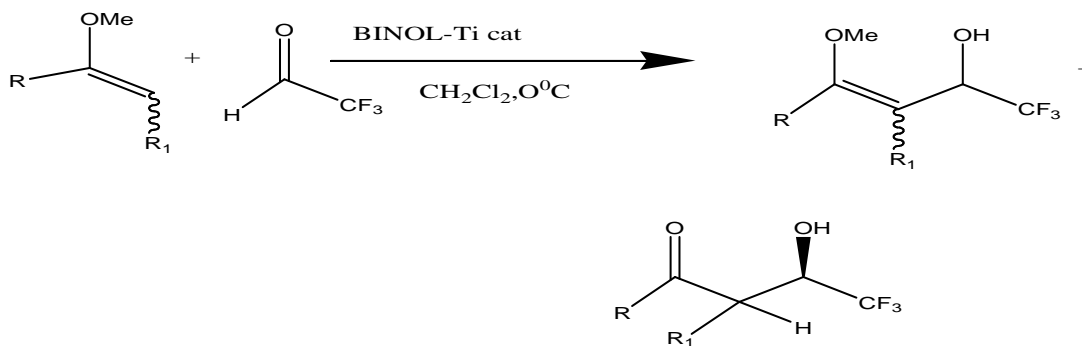
Whereas for catalyst (S)-1c the enantioselectivity is determined by the solvent effect.¹⁰



11. Asymmetric Friedel-Crafts reactions of vinyl ethers with fluoral catalyzed by chiral binaphthol-derived titanium catalysts.

Asymmetric Friedel-Crafts reactions of vinyl ethers with fluoral catalyzed by chiral

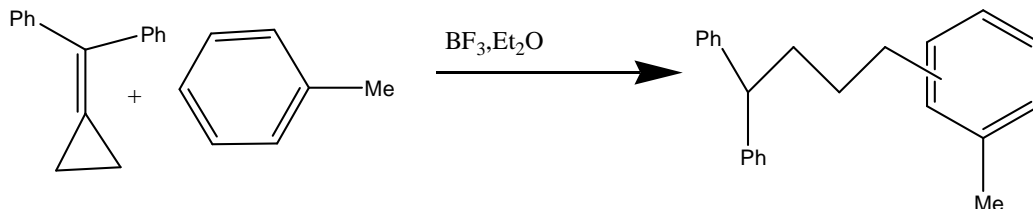
binaphthol-derived titanium catalysts gave reactive vinyl ether products. Sequential diastereoselective reactions of resultant vinyl ethers with *m*-CPBA provided highly functionalized organofluorine compounds in high enantiomeric purity.¹¹



Friedel-craft reaction of methyl vinyl ether with fluoral catalysed by BINOL-Ti catalyst

12. Lewis acid BF₃·OEt₂-catalyzed Friedel–Crafts reaction of methylenecyclopropanes with arenes.

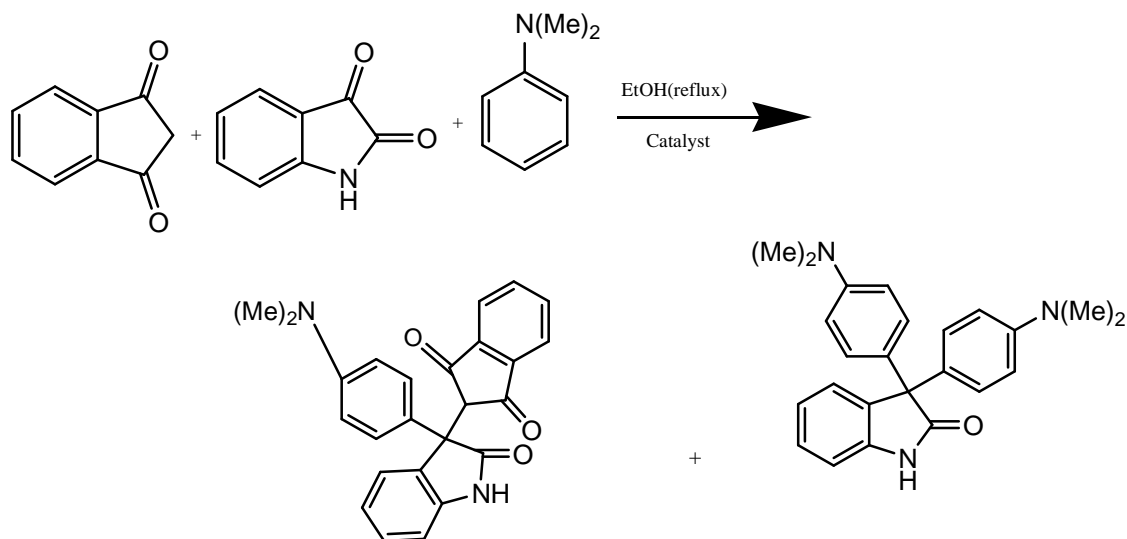
Methylenecyclopropanes react with various arenes to give the Friedel–Crafts reaction products in good yields in the presence of Lewis acid BF₃·OEt₂.¹²



13. Three-component synthesis of new unsymmetrical oxindoles via Friedel–Crafts type reaction.

The synthesis of 2-(3-(4-(dimethylamino)phenyl)-2-oxindolin-3-yl)-1H-indene-1,3(2H)-diones as new

unsymmetrical oxindoles via a Friedel–Crafts type three-component reaction of 1,3-indandione, N,N-dimethylaniline and isatins in ethanol in the presence of LiClO₄ is reported.¹³



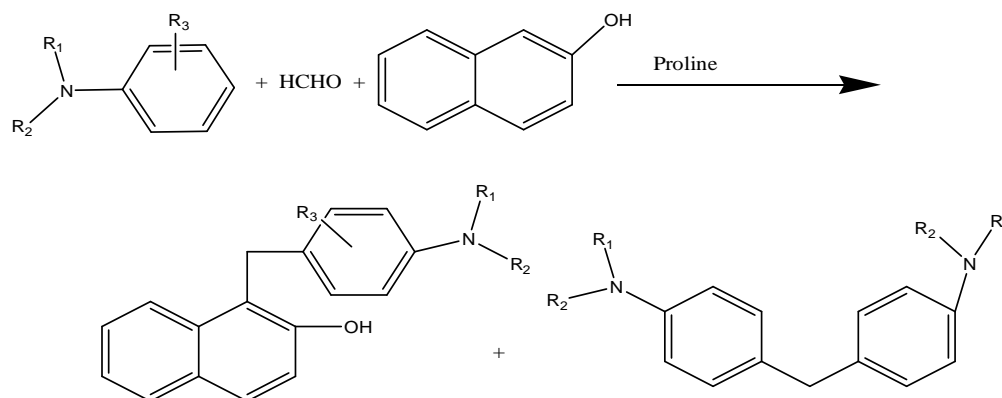
14. An efficient organocatalyzed multicomponent synthesis of diarylmethanes via Mannich type Friedel–Crafts reaction.

We have developed an efficient organocatalyzed, multicomponent synthesis of diarylmethane derivatives from tertiary

aromatic amines, formaldehyde and 2-naphthols via Mannich type Friedel–Crafts reaction. Several organocatalysts such as chinchonidine, L-proline, L-thiaproline, and L-pipecolic acid have been screened for the reaction but the best results were obtained with L-proline. In this Mannich type Friedel–

Crafts alkylation, tertiary aromatic amines react with formaldehyde–proline adduct to generate 1-(4-(dimethylamino) benzyl) pyrrolidinium-2-carboxylate intermediate,

which undergoes nucleophilic addition to give substituted diarylmethanes in excellent yields.¹⁴

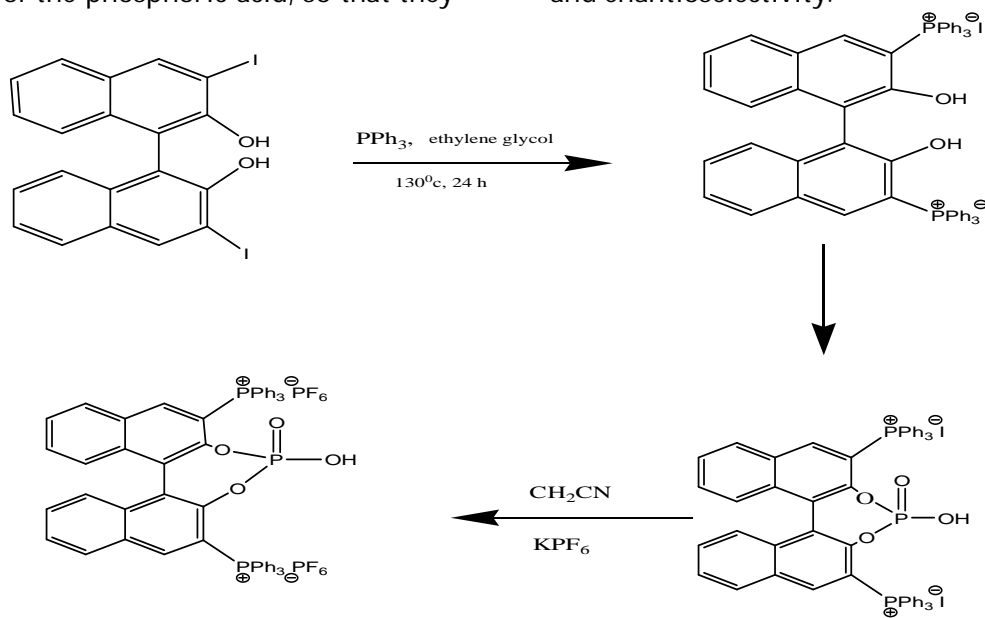


Synthesis of diarylmethane derivatives via Mannich type friedel-craft reaction

15. Phosphonium ion tagged chiral phosphoric acids and their application in FriedeleCrafts reactions of indoles.

The attachment of phosphonium ion phase tags to chiral binaphthyl-based phosphoric acid catalysts and the use of these materials in a range of organocatalytic asymmetric FriedeleCrafts reactions of indoles have been studied. Placement of the tags at the 3 and 30 positions of the phosphoric acid, so that they

could serve as steric blocking groups, failed to produce an active catalyst. However, moving the phosphonium ion groups to the 6 and 60 positions produced an efficient and enantioselective catalyst. Aided by the presence of the phase tags, the chiral catalyst was easily removed at the end of the reactions, and could be reused several times, albeit with somewhat decreased efficiency and enantioselectivity.¹⁵

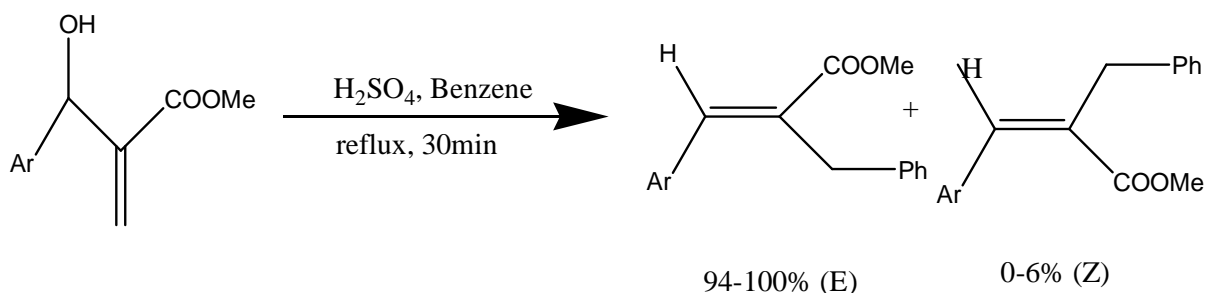


Synthesis of phosphonium ion tagged chiral phosphoric acid

16. One-pot inter- and intramolecular Friedel–Crafts reactions in Baylis–Hillman chemistry: a novel facile synthesis of (E)-2-arylideneindan-1-ones.

A simple one-pot stereoselective transformation of tert-butyl 3-aryl-3-

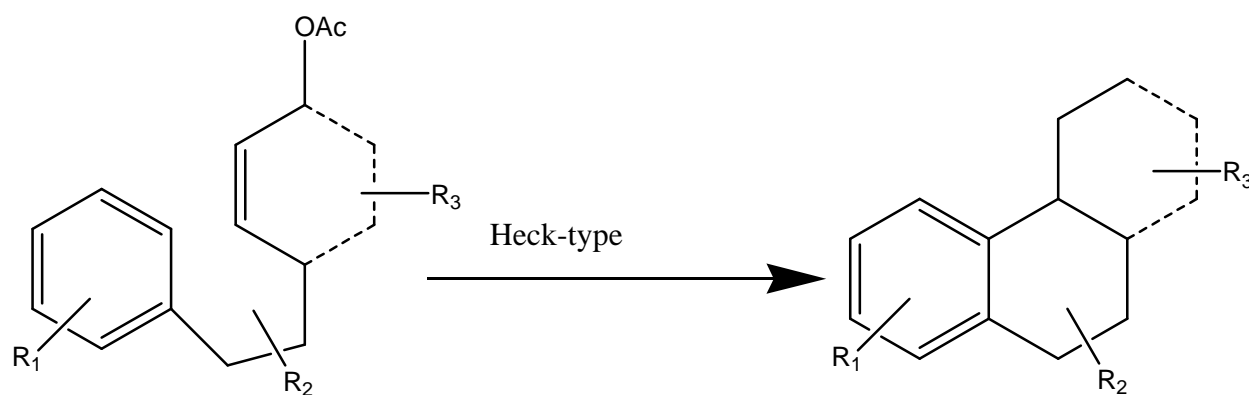
hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts obtained from t-butyl acrylate, into (E)-2-arylideneindan-1-ones involving one inter- and one intramolecular Friedel–Crafts reaction is described.¹⁶



17. TFA-mediated intramolecular Friedel–Crafts reaction. An efficient metal and halogen free route to stereoselective synthesis of benzocycles.

6-Acetoxy-4-alkenyl arenes undergo regio- and stereoselective intramolecular Friedel–Crafts reaction affording benzocycles in moderate to excellent yields in TFA/HOAc

(3:1). It was observed that introduction of alkyls or phenyl group to the allylic acetate moiety facilitates the cyclization reaction. The optically active tricyclic (4bR,8aS)-4b,7,8,8a,9,10-hexahydrophenanthrene skeleton could also be easily obtained in excellent yields.¹⁷



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