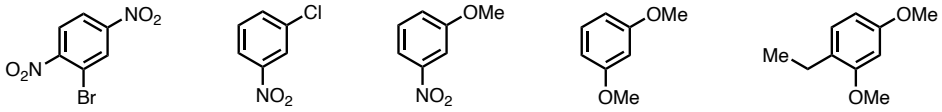
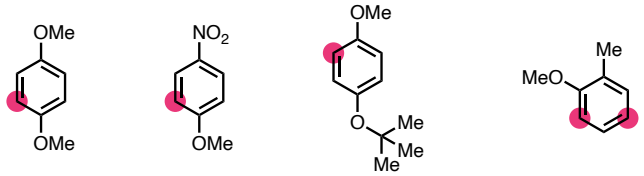
1. Order the following substrates according to increased reactivity toward Friedel-Crafts reactions. [★]



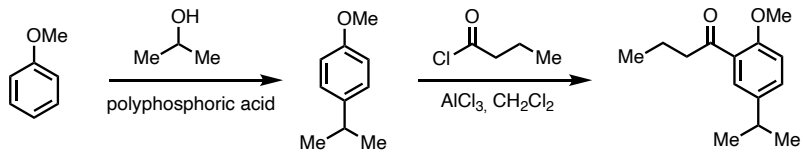
Friedel-Crafts type reactions follow the typical reactivity trends of electrophilic aromatic substitutions. The presence, number, and position of electron-donating and -withdrawing groups must be taken into account to assess the relative reactivity. Among the substrates bearing nitro groups (the most electron-withdrawing of the series), the one containing two and one bromide is the least activated, followed by the chloride-bearing one. In the third case, the *m*-MeO substitution mitigates the electron-withdrawing effect at the arene. Methoxy substituents are strongly activating towards Friedel-Crafts reactions, and further alkyl substitutions renders 1,3-MeO-4-ethylbenzene the most reactive.

2. Indicate the most activated position towards Friedel-Crafts reactions. [★]

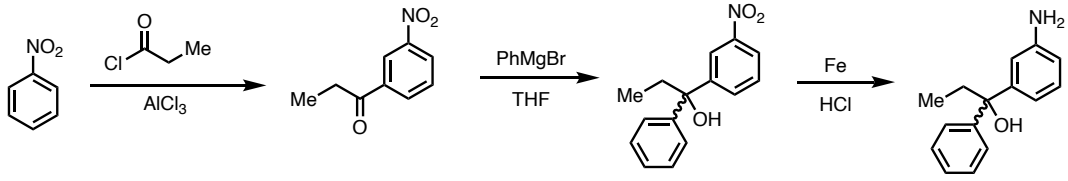


Friedel-Crafts type reactions follow the typical reactivity trends of electrophilic aromatic substitutions. Mesomerically-donating activating groups, such as methoxy and related ethers, are *ortho-para* directing. In the first case, all four positions are equally activated (one is indicated for simplicity). In the second case, the selectivity is dominated by the activating effect of the methoxy group, affording *ortho* selectivity. In the third instance, both alkoxy groups activate the arene system towards *ortho* reactivity, but the sterically demanding *tert*-butyl group renders its *ortho* position less susceptible to substitution (for a selectivity assessment with electrophilic aromatic nitrations, see: *Tetrahedron* **1974**, *30*, 3507-3511). In the fourth entry, the more activating methoxy group dominates the selectivity. Its *ortho-para* positions are preferentially functionalized, but it is not obvious if any preference between the two could be achieved.

3. Propose a synthetic strategy for each of the following retrosyntheses. [★★]



A possible synthesis is outlined above: anisole could undergo Friedel-Crafts alkylation (leading to a separable mixture of *ortho*/*para* isomers) using isopropanol and acidic catalysis (a close example: *J. Am. Chem. Soc.* **1954**, *76*, 4550). Other analogous alkylation protocols (e.g. from bromides or propene) are equally conceivable. The methoxy group offers the correct ring activation to achieve *ortho* acylation. Aluminum catalyzed conditions, as for example reported in patent WO2005/19151, can afford the correct isomer, with little competition from over-acylation (ring gets de-activated towards electrophilic aromatic substitutions).



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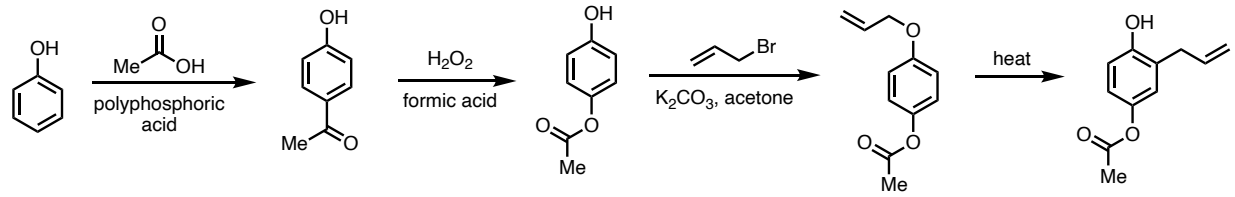
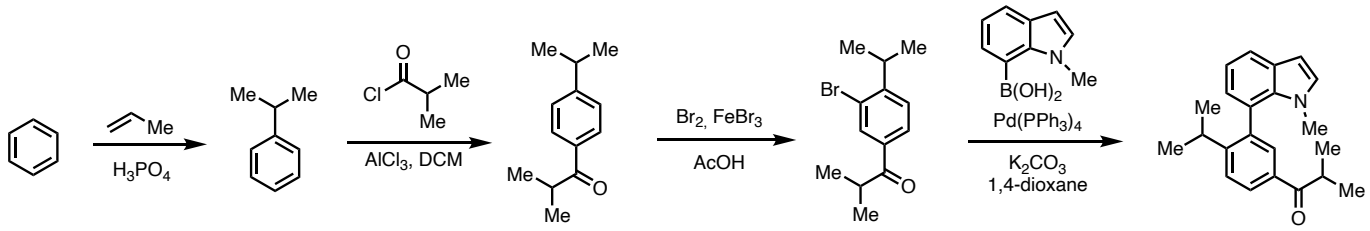
In order to achieve the desired *meta*-disubstitution, we can leverage the *meta*-directing effect of the nitro group. Friedel-Crafts acylation under vigorous Lewis acid catalysis can provide the corresponding aryl ketone. Alkylation of the ketone with an appropriate Grignard reagent can form the required tertiary alcohol (e.g. *J. Org. Chem.* **2005**, *70*, 6907-6912), without causing decomposition of the nitro group. The final step involves the iron mediated reduction of the nitro group to the corresponding aniline, under acidic conditions. Alternative conditions can involve catalytic hydrogenation using Ni-Raney or supported palladium.

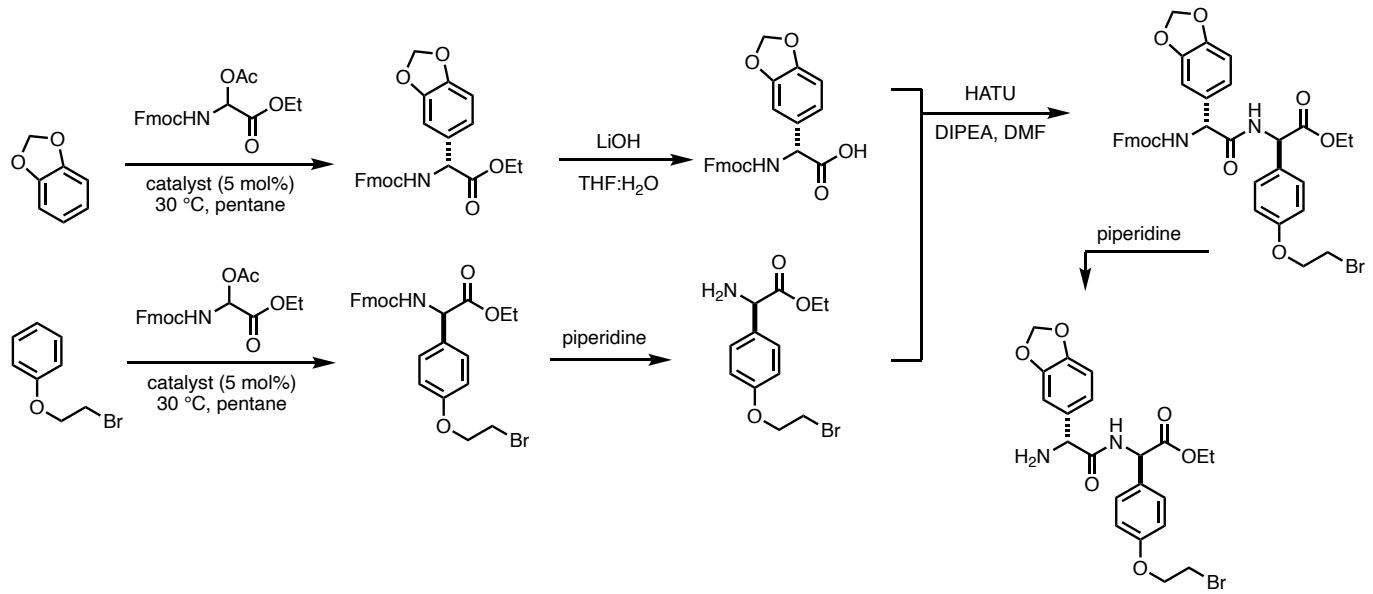


Phenol can undergo *para* Friedel-Crafts acylation under relatively mild conditions (e.g. *J. Am. Chem. Soc.* **1955**, *77*, 364), providing the corresponding acetophenone. The second step can involve a Baeyer-Villiger oxidation (conditions from patent WO2023/73080), which selectively afford the methyl ester product (aryl groups have higher migratory tendency, compared to methyl groups). The phenol moiety can be alkylated using allyl bromide under alkaline conditions and can be followed by Claisen rearrangement to afford the final product.

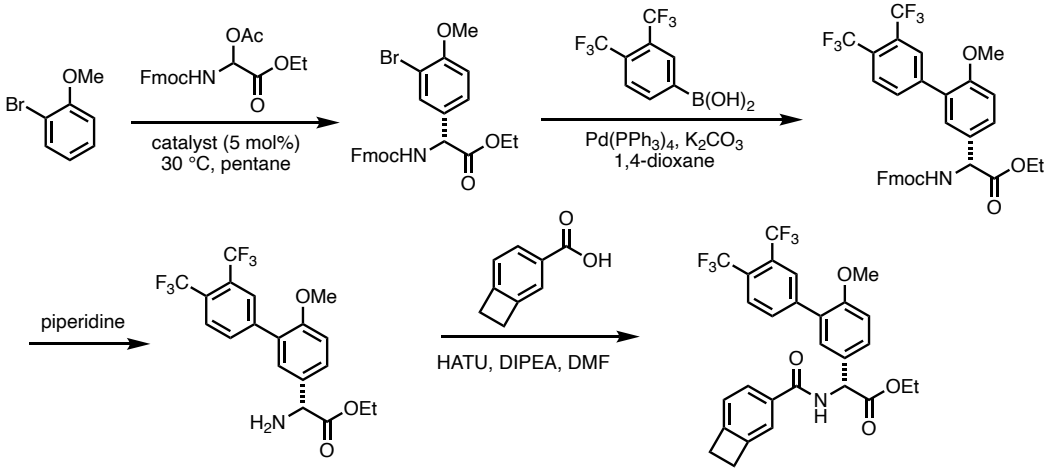


Benzene can be easily converted to cumene by alkylation with propene under acidic conditions (e.g. industrial cumene process). Cumene can undergo Friedel-Crafts acylation under acidic conditions to provide a mixture of *ortho-para* isomers (usually separable). *Ortho*-selective bromination can generate the required moiety to undergo Suzuki coupling with *N*-Me-indole 7-boronic acid to afford the final product.

4. Propose a synthesis of the following molecules (molecules are not reported in the paper, but similar substrates were successfully synthesized) using the strategy developed by List and co-workers (*J. Am. Chem. Soc.* **2023**, *145*, 15708–15713). [★★]

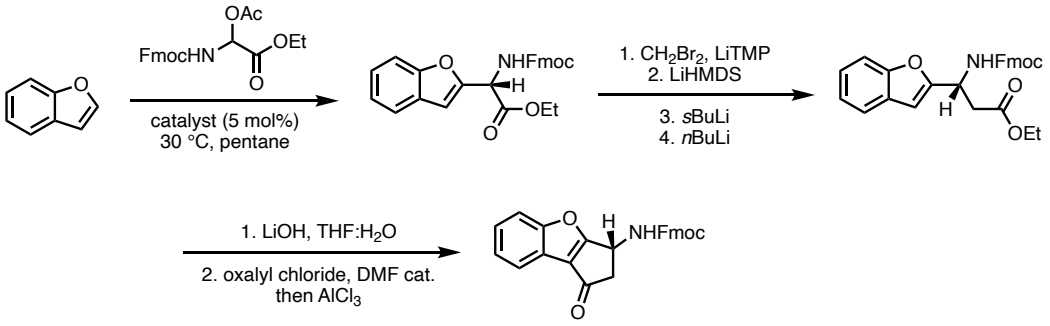


The first molecule requires a coupling of two amino-acidic fragments generated using the protocol by List and co-workers. Upon formation of the Fmoc-ester-protected benzodioxole fragment, basic hydrolysis delivers the free acid, which could be used as fragment in the final coupling. The bromoethyl ether fragment undergoes Fmoc cleavage by piperidine treatment, followed by amide coupling (HATU is used as coupling reagent).



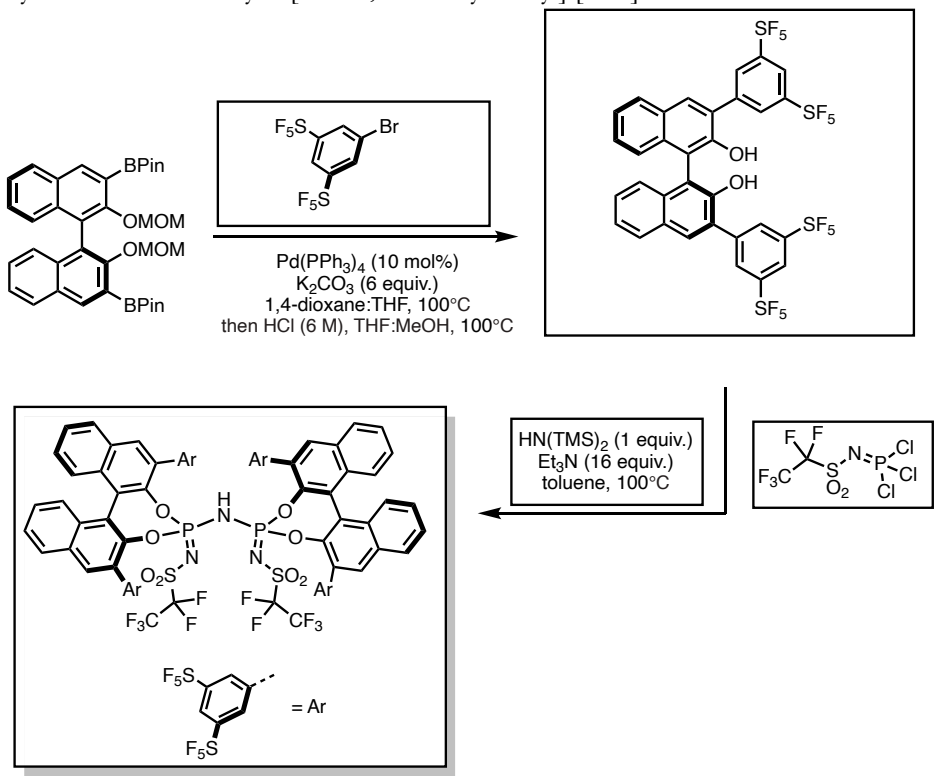
The molecule could be dissected by cleaving the amide bond, and the amino acidic fragments could be generated by combining the strategy by List and co-workers and palladium-catalyzed cross-coupling reactions. Starting from 2-bromoanisole, the Friedel-Crafts alkylation by List can produce the amino-acidic stereocenter. Cross-coupling with 3,4-CF_3-phenylboronic acid under palladium cross-coupling can generate the substituted biphenyl moiety. The Fmoc group is cleaved using piperidine, and final amide coupling delivers the final product.

5. Propose a synthesis of the following molecule molecules (the molecule is not reported in the paper, but similar substrates could be successfully synthesized) using the strategy developed by List and co-workers (*J. Am. Chem. Soc.* **2023**, *145*, 15708–15713). [Fmoc, fluorenylmethoxycarbonyl] [★★★]



The five-membered ketone system in the product requires a homologation reaction to achieve the required connectivity from a product of the Friedel-Crafts reaction developed by List and co-workers. Upon formation of the protected amino-acid, a Kowalski ester homologation strategy can be employed to elongate the chain. Basic ester hydrolysis, followed by chlorination and Friedel-Crafts acylation, can provide the product.

6. Complete the synthesis of the catalyst. [MOM, methoxymethyl] [★★]



The first step involves a Pd-catalyzed Sukuzi coupling, formed by one-pot cleavage of the 2,2'-methoxymethyl groups under acidic conditions. Treatment with bis-TMS-amine under basic condition generates the final product.