FULL PAPER

Catalytic Friedel-Crafts Reactions on Saturated Heterocycles and Small Rings for sp^3-sp^2 Coupling of Medicinally Relevant Fragments

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Abstract: *gem*-Diarylheterocycles display a wide range of biological activity. Here we present a systematic study into the formation of 4- to 6-membered O- and N-heterocycles and cyclobutanes bearing the diaryl motif through a catalytic Friedel–Crafts reaction from the corresponding benzylic alcohols. 3,3-Diaryltetrahydrofurans, 4,4-diaryltetrahydropyrans, 3,3-diarylpyrrolidines, 4,4-diaryl-piperidines, as well as diarylcyclobutanes are examined, with results for 3,3-diaryloxetanes and 3,3-diarylazetidines presented for comparison. Three catalytic systems are investigated for each substrate [Ca(II), Li(I) and Fe(III)], across preinstalled aromatic groups of differing electronic character. In most cases examined, the diaryl product is obtained directly from the alcohol with good yields using the most appropriate catalyst system. In the absence of a nucleophile, the olefins from the 5- and 6-membered substrates by elimination of water are obtained under the same reaction conditions.

Introduction

The synthesis of saturated heterocycles is of crucial importance in the preparation of new medicines, with 5- and 6-membered saturated oxygen and nitrogen heterocycles among the most prevalent motifs in biologically active molecules.[1] These polar substructures present high 3-dimensional character, which can have advantages in solubility and complementary topology for biological targets.[2] Similarly, 4-membered ring derivatives are attractive due to defined exit vectors and unusual structural features, which can lead to improved metabolic stability, and more readily access new chemical and intellectual property space.[3] The combination of saturated heterocycles with aromatic substituents provide particularly attractive screening compounds as fragments or lead-like compounds due to the different potential binding interactions available. However there remain challenges in readily accessing a broad array of substituted heterocycles under mild conditions, as is appropriate in divergent and iterative medicinal chemistry investigations.[4] The sp^3-sp^2 coupling of small rings or saturated heterocycles with aromatic components presents a valuable transformation that can facilitate the construction of important compound types in drug discovery.

gem-Diaryl substituted saturated O- and N-heterocycles are frequently reported in biologically relevant molecules, often in the patent literature (Figure 1).[5-12]

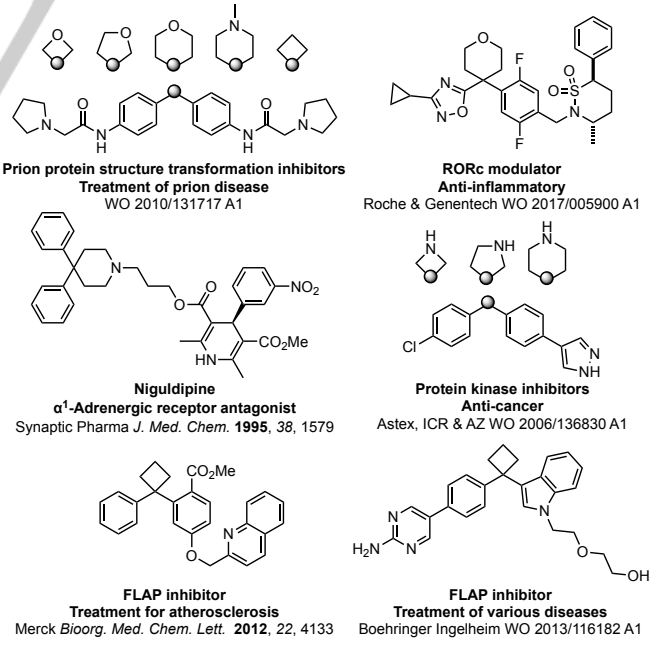

Figure 1. Example biologically active heterocycles and small rings with *gem*-diaryl groups.

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Supporting information for this article is given via a link at the end of the document. All characterization data for synthesized compounds can be found at https://doi.org/10.14469/hpc/5166.

Examples include prion-protein interaction inhibitors bearing diaryl-oxetane, -THF, -THP, -piperidine and -cyclobutane motifs.[5] A 4,4-diaryltetrahydropyran is present in a retinoid-receptor related orphan receptor RORc modulator developed by Roche and Genentech,[6] but there remain few examples of this type. There are more examples of 4,4-diaryl-piperidines,[7,8] a notable case being Niguldipine, a calcium channel blocker and α^1-adrenergic receptor antagonist.[9] Kinase inhibitors featuring 3,3-diarylazetidines, pyrrolidines and 4,4-diarylpiperidines have been developed by Astex, AZ and the ICR.[10,11] Diarylcyclobutanes have been developed by Merck and Boehringer Ingelheim, both as 5-lipoxygenase activating protein (FLAP) inhibitors.[12]

There are few general methods for the synthesis of these *n,n*-diaryl-rings.[13-20] 3,3-Diaryltetrahydrofurans have been prepared by reduction of the corresponding lactone,[13] or cyclization of a suitable diol.[14] Common routes to 3,3-diaryl-pyrrolidines are the intramolecular hydroamination of alkenylamines,[15] or the reduction of pyrrolidinones using $LiAlH_4$.[16] 4,4-Diaryl-tetrahydropyrans have been accessed through Friedel–Crafts reactions with electron rich aromatics using $FeCl_3$ or TfOH.[17] To access 4,4-diarylpiperidines, Friedel–Crafts reactions using strong acids or $AlCl_3$ from the corresponding piperidinone or piperidinol have been employed extensively.[18] Alternatively, dehydration of the piperidinol to an intermediate alkene has been shown to undergo arylation with phenols on treatment of $BF_3{\cdot}Et_2O$.[19] Diarylcyclobutanes have been synthesized by a Friedel–Crafts reaction using $FeCl_3$ or $InBr_3$ in catalytic or stoichiometric quantities,[12a] and by a [2+2] cycloaddition followed by reduction of the resulting cyclobutanone.[12b]

Methods for catalytic Friedel–Crafts reactions have seen extensive development in recent years, allowing the use of π-activated alcohols as substrates (Figure 2a).[21,22] Catalytic Friedel–Crafts reactions on heterocyclic alcohols, however, remain under-studied, with little known about their relative reactivity or optimal catalytic systems. Friedel–Crafts methods on heterocyclic alcohols have typically used stoichiometric strong Brønsted or Lewis acids, which can limit functional group compatibility.

We have been interested in saturated oxygen and nitrogen heterocycles bearing *gem*-diaryl groups, towards novel isosteres and linking groups for use in medicinal chemistry. We recently reported methods for the synthesis of 3,3-diaryloxetanes[23] using oxetanols with phenols and a lithium triflimide catalyst (Figure 2b). Under related conditions, we reported Li-catalyzed thiol alkylation procedures with oxetanols.[24] We also reported 3,3-diarylazetidines by Friedel–Crafts alkylation of electron rich aromatics with azetidinols, where a calcium triflimide catalyst was optimal (Figure 2b).[25] On the other hand, very recently we have shown that thiol alkylation with azetidinols proceeds most efficiently with an $FeCl_3$ catalyzed procedure.[26]

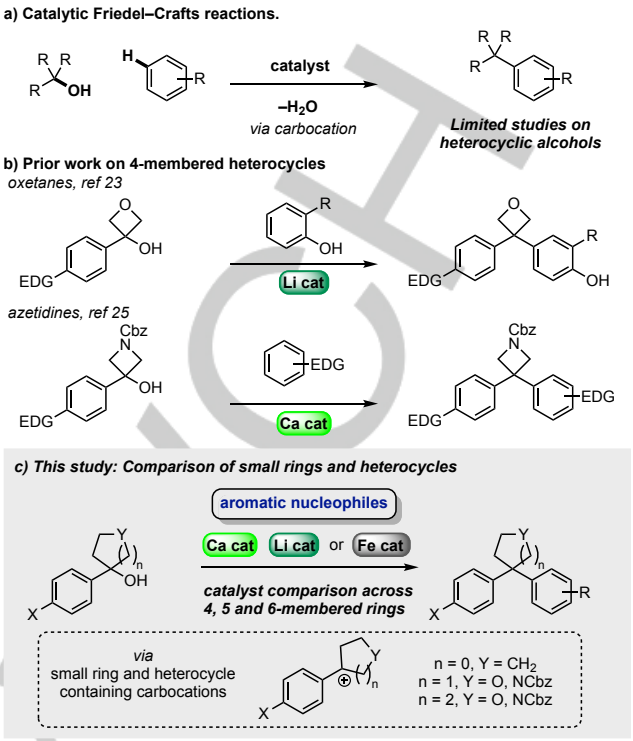


Figure 2. Previous work on the catalytic preparation of diaryloxetanes and diarylazetidines, and this work on catalytic Friedel-Crafts reactions on heterocycles.

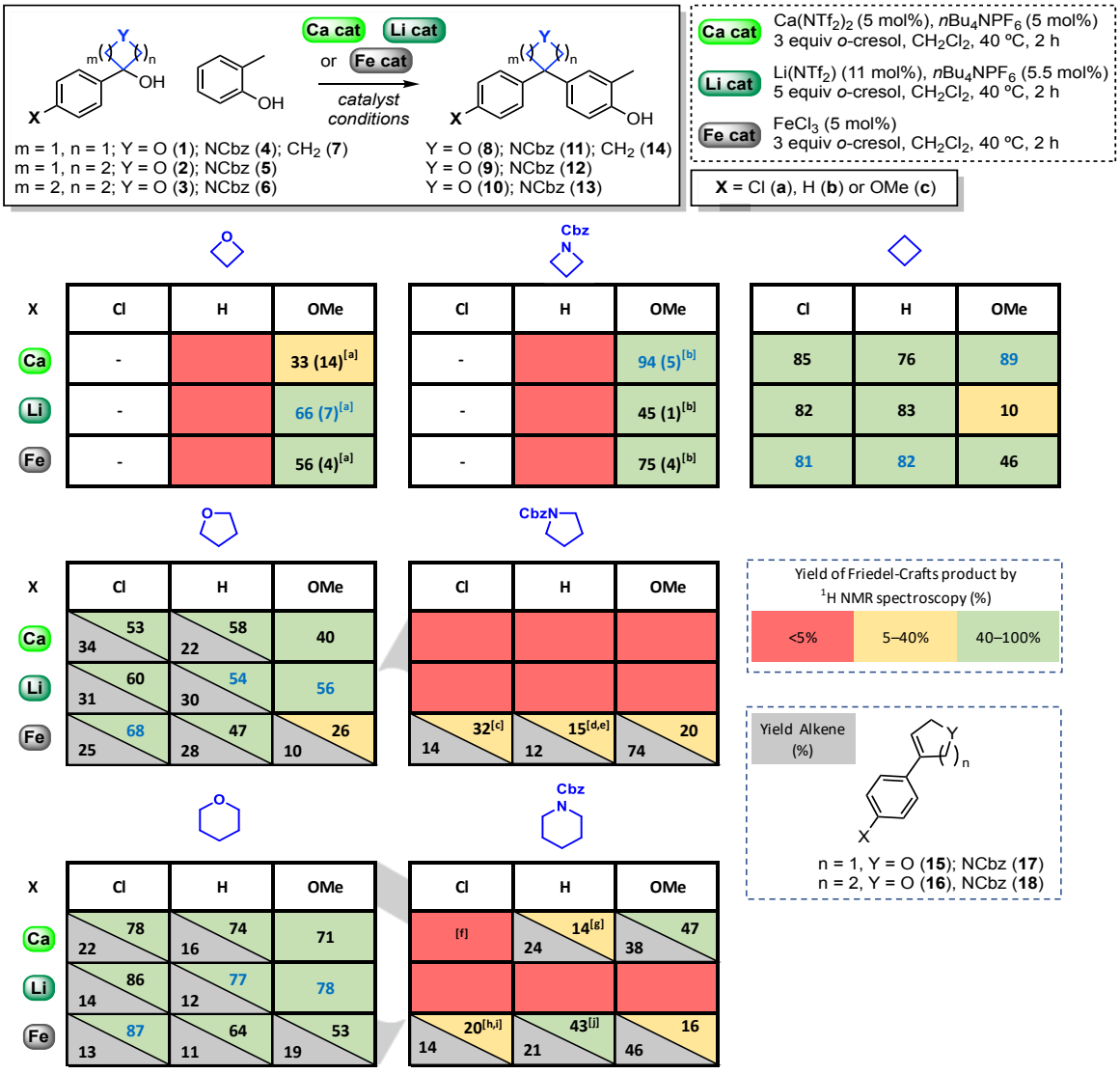
Given the importance of the diaryl-heterocycle motif in medicinal chemistry, and building on our prior work, we targeted milder catalytic methods for the preparation of non-symmetrical *n,n*-diarylheterocycles. Here we report a study into catalytic Friedel–Crafts reactions with a broader range of heterocycles and small rings (Figure 2c). In particular, we present a systematic comparison of mild Lewis acid catalysts derived from calcium(II), lithium(I) and iron(III) salts based on successes in our prior work, across a range of 4-membered rings (oxetane, azetidine, and cyclobutane), as well as 5- and 6-membered oxygen and nitrogen heterocycles.

Results and Discussion

The initial objective was to systematically compare catalyst types and quantify the reaction outcomes in the Friedel–Crafts reactions with aryl-substituted oxetan-3-ols, tetrahydrofuran-3-ols and tetrahydropyran-3-ols, as well as for azetidin-3-ols, pyrrolidin-3-ols, piperidin-4-ols, and cyclobutanols. We examined Li, Ca and Fe catalysts, chosen to represent different Lewis acidic metals considered to be relatively environmentally benign and sustainable. These Lewis acid catalysts were also those previously shown to be reactive with oxetane and azetidine substrates.[23-26] Cyclic tertiary alcohol substrates **1**–**7** were prepared from the corresponding commercially available ketones by the addition of the aryllithium or Grignard regents.[27] To

compare the effect of the electronic properties of the aromatic stabilizing group substrates were prepared with 4-chlorophenyl (**a**), phenyl (**b**), and 4-methoxyphenyl (**c**, PMP) substituents. Three sets of conditions were defined to compare the catalyst types, each using *o*-cresol as the nucleophiles in CH_2Cl_2 at 40 °C for 2 h, as defined in Scheme 1. Scheme 1 presents results of the reactions conducted on each of these substrates with each of the conditions defined, providing a visual comparison, with yields measured by ^{1}H NMR spectroscopy against an internal standard.

O-Heterocycles. The study started with oxetane derivatives **1**. As was previously observed,[23a] the Friedel–Crafts reaction was successful with PMP-substituted oxetanol **1c** with each of the three catalyst systems. The lithium triflimide/nBu$_4$NPF$_6$ catalyst system was most effective, though the reaction was marginally lower yielding in CH_2Cl_2 rather than $CHCl_3$ as used in our previous report. With less electron rich aromatic derivatives (including Ph) the reaction was unsuccessful. This reflects the increased strain



X	Cl	H	OMe
Ca	-		33 (14)[a]
Li	-		66 (7)[a]
Fe	-		56 (4)[a]

Cl	H	OMe
-		94 (5)[b]
-		45 (1)[b]
-		75 (4)[b]

Cl	H	OMe
85	76	89
82	83	10
81	82	46

X	Cl	H	OMe
Ca	53 / 34	58 / 22	40
Li	60 / 31	54 / 30	56
Fe	68 / 25	47 / 28	26 / 10

Cl	H	OMe
32[c] / 14	15[d,e] / 12	20 / 74

X	Cl	H	OMe
Ca	78 / 22	74 / 16	71
Li	86 / 14	77 / 12	78
Fe	87 / 13	64 / 11	53 / 19

Cl	H	OMe
[f]	14[g] / 24	47 / 38
20[h,i] / 14	43[j] / 21	16 / 46

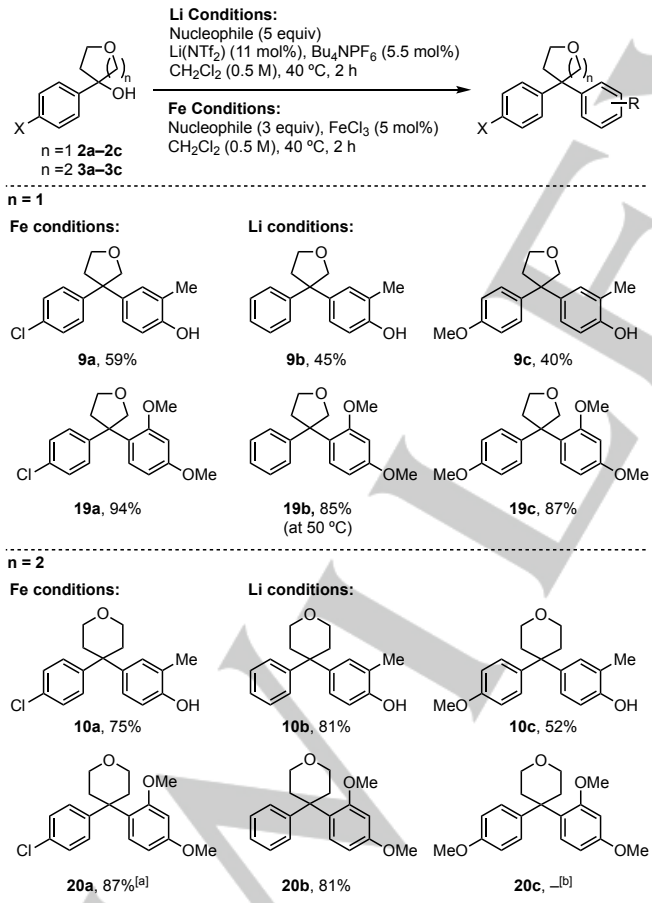
Scheme 1. Comparison of yields of Friedel–Crafts products and olefin elimination products across different small rings and heterocycles with varied catalyst systems. Yields measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Those highlighted in blue correspond to conditions used in schemes 2, 3, and 5. [a] Yield in parentheses corresponds to the dihydrobenzofuran resulting from cyclization of the *ortho*-substituted product with oxetane opening (see ref 23). a). [b] Yield in parentheses corresponds to the *ortho*-substituted product. [c] A 24 h reaction time gave 67% diaryl **12a** (29% alkene **17a**). [d] 64% recovered starting material **5b**. [e] A 24 h reaction time gave 46% diaryl **12b** (30% alkene **17b**) [f] No reaction at 40 °C. Performing the reaction at 50 °C gave 50% diaryl **13a** (47% alkene **18a**). [g] 56% recovered starting material **6b**. [h] 69% recovered starting material **6a**. [i] Performing the reaction at 50 °C (2h) gave 70% diaryl **13a** (29% alkene **18a**). [j] 24% recovered starting material **6b**.

on generating the 4-membered ring carbocation and the inductive electron-withdrawal from the oxygen atom increasing the activation barrier, resulting in no reaction in the absence of the strongly stabilizing aromatic group.

The THF and THP derivatives were more reactive than the oxetanes, and less significantly influenced by the substituents on the aryl group. However, for both the 5- and 6-membered rings, olefin products from the elimination of water (**15**, **16**) were observed (in grey, Scheme 1). Elimination products were not observed in the 4-membered ring derivatives, but there was evidence for their formation from decomposition products,[23b] and it is likely this pathway led to a loss of yield.

For the THF derivatives the results were largely similar with the different catalysts. For the chloro-derivative **2a**, the use of $FeCl_3$ gave the best result, but calcium and lithium gave better yields for the phenyl and methoxy-derivatives (**2b,c**). This same trend was observed for THP derivatives **3a–c**.

Isolated yields were obtained for the THF and THP derivatives using *o*-cresol and 1,3-dimethoxybenzene (1,3-DMB) as nucleophiles, to cover different nucleophile classes (Scheme 2). In selecting the catalyst to use, we prioritized yield, and cost where results were the same for 2 different catalysts in Scheme 1. We selected Fe>Li>Ca due to the cost of these catalysts, i.e. favoring Fe catalysis where appropriate.



Scheme 2. Catalytic Friedel–Crafts reactions to form diaryl-THFs (n = 1) and diaryl-THPs (n = 2). Isolated yields quoted. [a] Used 5 equiv nucleophile. [b] No reaction occurred at 40 °C; degradation at 50 °C.

Using $FeCl_3$ in a preparative reaction using 4-chlorophenyl-THF **2a** gave a 59% isolated yield of **9a** when using *o*-cresol, in good agreement with the screening results. 1,3-Dimethoxybenzene led to a high yield of the diaryl product **19a**. The Li catalyst was selected for phenyl and PMP derivatives, also giving slightly higher yields when using 1,3-DMB vs *o*-cresol. Interestingly however, the use of 1,3-DMB to form phenyl derivative **19b**, repeatedly gave low reactivity under the usual conditions, but the isolated yield was increased to 85% by performing the reaction at 50 ºC. The alkenes formed by elimination were significant side products in all of the cases using the phenolic nucleophile. It is notable that this was much less significant with the 1,3-DMB nucleophile, suggesting the phenol contributes to the elimination. With example **19c**, the reaction was performed both in dichloromethane and toluene giving 87% and 80% respectively, demonstrating the potential to use more environmentally benign solvents. Running this same reaction with 1.5 equivalents of nucleophile (rather than 5) still gave a good yield of 75% (by ^{1}H NMR; with no recovered starting material), on this relatively activated substrate.

High yields were obtained for all THP substrates with both nucleophiles under the selected conditions (Fe for X = Cl; Li for X = H, OMe), with the more distal oxygen atom having a reduced destabilizing effect on the carbocation. However, the reaction of THP **3c** with DMB was unsuccessful, which yielded only starting material at 40 ºC and increasing the temperature led to decomposition.

NCbz-Heterocycles. The 4- to 6-membered N-heterocyclic alcohols **4**–**6** were assessed as carbamate protected derivatives due to the synthetic flexibility and ease of removal of the carbamate group. In our prior studies on azetidines, the NCbz-group was uniquely reactive, with no reaction occurring on the NBoc derivative.[25,26] We proposed a π-cation stabilizing interaction between the phenyl group of the Cbz group and the azetidine carbocation. Preliminary results for the NBoc pyrrolidinol and piperidinol derivatives were also significantly less reactive than the Cbz derivatives, with increased elimination, especially in the 6-membered ring (see later). Hence, studies focused on the Cbz protecting group. As for oxetanes, the reaction with the azetidine derivatives was successful with electron-donating aromatic groups installed (Scheme 1). For PMP derivative **4c**, the Ca and Fe catalysts were most appropriate, with excellent yields and *ortho*/*para*-selectivity observed using calcium triflimide/*n*Bu_4NPF_6.[25]

For the synthesis of 3,3-diarylpyrrolidines, $FeCl_3$ was the only catalyst which gave a successful reaction (Scheme 1). Under the standard conditions, low yields of **12a-c** were obtained, along with similar quantities of the elimination product. For the chlorophenyl and phenyl examples, significant starting material was observed. Extending the reaction time to 24 h for **5a** (Cl) and **5b** (H) gave 67% of arylated product **12a**, (29% alkene **17a**) and 46% **12b** (30% alkene **17b**) respectively as determined by ^{1}H NMR spectroscopy.

To isolate the diarylpyrrolidines for X = Cl or H (**12a,b** and **21a,b**), the reaction was run for 24 h and good yields were obtained for the desired product with both nucleophiles (Scheme 3, n = 1). The more stable carbocation, when X = OMe, was more readily formed and full conversion was achieved in 2 h. High yield was obtained for the formation of **21c** with 1,3-DMB but for

o-cresol, only 16% of **12c** was observed with a much higher proportion of elimination product **17c**.

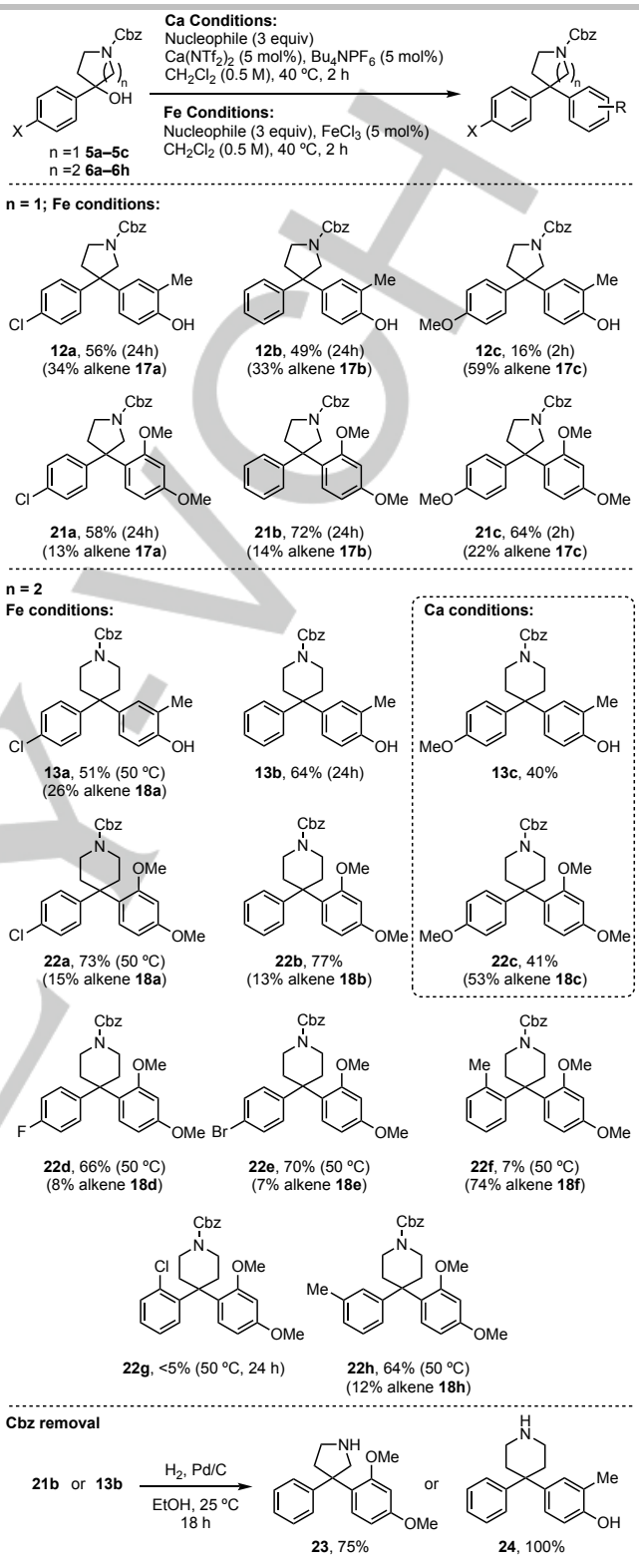
Similar to the oxygen series, the 6-membered piperidine derivatives generally gave higher yields than the 5-membered pyrrolidines (Scheme 1). For the Ph and PMP substrates **6b** and **6c** the Friedel–Crafts reaction was achieved with the Ca catalyst. The chloro-derivative **6a** was unreactive using Ca under the standard conditions at 40 ºC, but at 50 ºC gave a 50% yield. The lithium catalyst was unreactive for all substrates. Using $FeCl_3$ did give reaction of **6a** and **6b** at 40 ºC, though unreacted starting material remained: running the reaction on **6a** at 50 ºC gave much improved conversion in the 2 h time period.

Preparation of the 4,4-diarylpiperidines using *o*-cresol and 1,3-DMB gave a good yield of compounds **13a-c** and **22a-c** (>40%, average yield 58%) using the Fe and Ca catalyst systems as appropriate (Scheme 3, n = 2). Given the occurrence of such motifs in medicinal chemistry, additional examples were investigated with 1,3-DMB, changing the pre-installed aromatic group (**22d–h**). The introduction of the 4-fluoro or 4-bromophenyl derivatives were similarly well tolerated (**22d** and **22e**), with the latter providing a handle for further derivatization. A 2-methylphenyl derivative gave low yield of **22f** at 50 ºC with elimination predominating (74% isolated yield of **18f**), presumably due to the *ortho*-substituent affecting the approach of the nucleophile. On the other hand, 2-chlorophenyl gave <5% isolated yield **22g** at 50 ºC for 24h with the majority as recovered starting material, due to the increased influence of the inductive electron withdrawal from the chloride. 3-Methylphenyl derivative **22h** was formed in good yield.

The deprotection of the Cbz group was demonstrated on **21b** and **13b** under standard conditions using H_2 and Pd on carbon, to provide **23** and **24** as valuable scaffolds suitable for further functionalization, and themselves closely related to biologically active pharmacophores.[28]

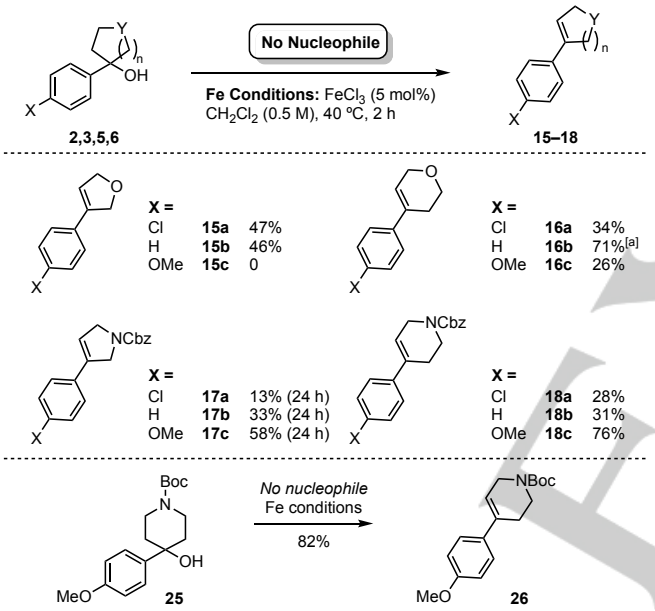
It is again noticeable that the phenol nucleophiles resulted in lower yields and increased elimination than 1,3-DMB, despite being more electron-rich species, and commonly more reactive for Friedel–Crafts reactions. We can speculate that this is due to interaction of the catalyst with the phenol, perhaps leading to increased Brønsted acidity of the phenols, and unproductive elimination reactions. Alternatively, the phenol may be providing a base to effect elimination.

Furthermore, it is clear that the electronic characteristics of the aromatic group influence the extent of elimination, with the most electron rich PMP derivatives giving most elimination in the N-heterocycle series. The carbocation being more readily formed, and presumably more stable, does not equate to improved reactivity with the nucleophile, and the factors for high yield are more subtle. Attempts to re-subject the elimination products to the reaction conditions did not form the diarylheterocycles, as has been possible using $BF_3{\cdot}Et_2O$ as a Lewis acid.[19]



Scheme 3. Catalytic Friedel–Crafts reactions to form diarylpyrrolidines (n = 1) and diarylpiperidines (n = 2), and Cbz deprotection. Isolated yields quoted.

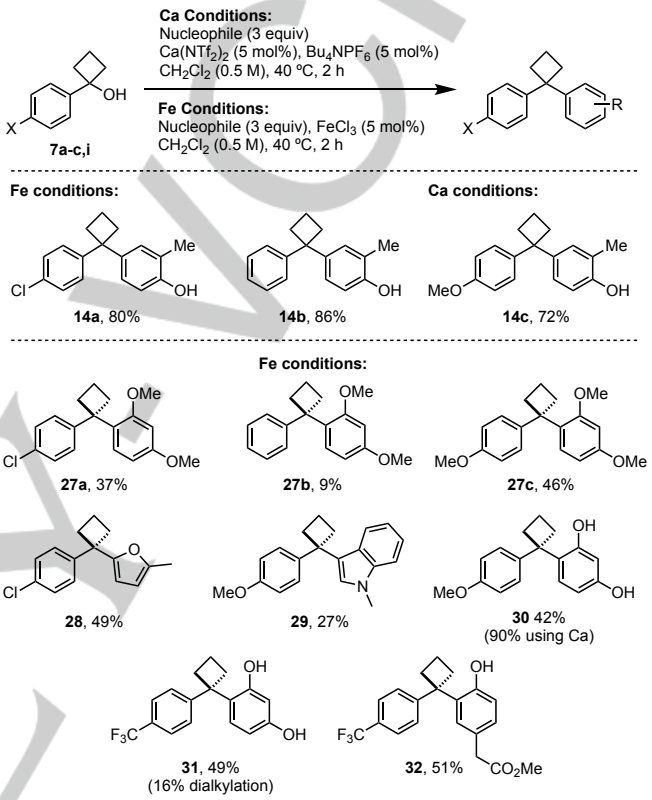
Heterocyclic alkene. Given the value of such heterocyclic alkenes to prepare alternative heterocyclic derivatives by reaction of the alkene, we examined their formation.[29] Related dehydration reactions are commonly achieved in presence of acid, though there are few examples of Lewis acid catalyzed dehydration on these types of substrates.[30,31] The reaction of each heterocycle derivative **2**, **3**, **5** and **6** was investigated in the absence of the nucleophile, using $FeCl_3$ as catalyst (Scheme 4). In most cases, the 3,4-unsaturated derivative was isolated in useful yields. Interestingly, for the PMP-THF derivative, decomposition of the product occurred under the Fe and Ca catalyzed conditions. This may be through isomerization to the 2,3-olefin (which is not observed in any example) followed by hydrolysis. During preliminary investigations with the N-Boc derivatives, the ease of elimination was noted. Here, using N-Boc PMP piperidinol **25**, a high yield of **26** was obtained in the absence of the nucleophile.



Scheme 4. Iron catalyzed elimination of water from heterocyclic alcohols. Isolated yield quoted. [a] using Li catalyst.

Cyclobutanes. Cyclobutanes are known to have enhanced carbocation stability due to a transannular stabilizing σ_{CH}–p interaction.[32] Indeed, the increased reactivity vs oxetane and azetidine derivatives was clear, and each catalyst system was effective for all cyclobutanols (**7**) tested (Scheme 1).[33] It was notable that the PMP derivative **7c** was most sensitive to the change in catalyst, with the Ca catalyst preferred.

Under the preferred catalyst systems, the 3,3-diarylcyclobutanes **14a–c** were obtained in high yield when using *o*-cresol as the nucleophile (Scheme 5). When using 1,3-DMB, the yields were low (**27a–c**), which reflected the difficulty in chromatographic separation of the lipophilic product from the excess nucleophile, not the efficiency of the reaction in itself. Heteroaromatic nucleophiles such as 2-methylfuran and *N*-methylindole were successful under the $FeCl_3$ catalyzed conditions (**28** and **29**). More polar nucleophiles such as 1,3-resorcinol avoided purification issues and gave good yields for the 3,3-diarylcyclobutanes. Using $FeCl_3$ to form **30** from PMP-cyclobutanol **7c** with resorcinol was successful, though the Ca catalyst, gave a higher yield as would be predicted based on Scheme 1. The higher reactivity of the cyclobutanols enabled strongly electron-withdrawing substituent 4-CF_3 to be included, to generate resorcinol derivative **31** and a methylacetate substituted phenol, **32**, through *ortho*-substitution in good yield.



Scheme 5. Catalytic Friedel–Crafts reactions to form diarylcyclobutanes. Isolated yields quoted. **7i** corresponds to 4-trifluoromethylphenylcyclobutanol.

Conclusions

Catalytic Friedel–Crafts reactions can be used to install *gem*-diaryl motifs on diverse ring systems, using tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine and cyclobutane derived substrates. The reactions using mild Lewis acids proceed successfully to form the diaryl derivatives providing an sp^3-sp^2 coupling from the alcohol substrates, with water as the only side-product. This work reports a systematic comparison of catalysts and substrates, varying ring type and aryl substituent. 40 Examples of *gem*-diaryl heterocycles are isolated, all as novel compounds, as well as 12 alkenyl derivatives, formed by elimination of water from the alcohol substrates in the absence of the nucleophile. Conditions were presented to provide a comparison of substrates, and to assess the potential of this approach, though it is likely that focused optimization for a particular target compound may afford improved yields and allow reduced excess of nucleophile, or alternative solvents.

In several cases the use of $FeCl_3$ is shown to be the most effective catalyst, particularly for more electron poor aromatic groups, compared with lithium triflimide/nBu$_4$NPF$_6$ or calcium triflimide/nBu$_4$NPF$_6$ systems which were more appropriate for electron-rich aromatic derivatives. As previously reported, oxetane and azetidine derivatives are successful with electron donating substituents, with lithium and calcium catalysts respectively preferred. The 5- and 6-membered oxygen heterocycles were more reactive, and gave generally high yields for both *o*-cresol and 1,3-dimethoxybenzene nucleophiles. The N-heterocycles, bearing the Cbz protecting group, were more sensitive to catalyst type, and required higher temperature or reaction time to achieve full conversion. For the 5- and 6-membered heterocycles, PMP derivatives gave a lower yield for the Friedel-Crafts reaction, due to increased elimination or decomposition, despite affording more stabilized carbocations. It is clear the nature of the nucleophile has an effect on yield. Indeed, the less electron rich 1,3-dimethyoxybenzene nucleophile gave better results, consistent with the phenol nucleophile promoting an irreversible elimination. Finally, aryl-cyclobutanols were effective substrates for a range of catalysts. Iron chloride was preferred and shown to be suitable for electron rich and electron poor installed aromatics (including trifluoromethyl).

Overall, this approach provides a useful strategy for the preparation of non-symmetrical *gem*-diaryl heterocycle derivatives. It is clear there is not a direct correlation from catalyst system to the different ring sizes, hence this study may provide a useful guide for medicinal and synthetic chemists attempting to access similar heterocyclic derivatives.

Experimental Section

General Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (CH_2Cl_2, THF) or used as supplied. Flash column chromatography was performed using 230-400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution or a ninhydrin solution in ethanol. Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ = 7.27 ppm, DMSO: δ = 2.50 ppm, CD_3OD: δ = 3.35 ppm, $(CD_3)_2CO$: δ = 2.05 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet and br = broad], coupling constant (in Hz), integration and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, CD_3OD: δ = 49.0 ppm, $(CD_3)_2CO$: δ = 29.84 ppm). Assignments of ^{1}H and ^{13}C spectra were based upon the analysis of δ and J values, as well as DEPT, COSY and HSQC experiments where appropriate. All carboxybenzyl (Cbz) containing compounds appeared as a mixture of rotamers in the NMR spectra at rt. Melting points were recorded using Optimelt MPA100 apparatus and are uncorrected. ^{19}F NMR spectra were recorded with or without complete proton decoupling. Decoupling is indicated as ($^{19}F\{^1H\}$) and where relevant this is stated in each assignment and spectrum. ^{19}F NMR spectra are indirectly referenced to $CFCl_3$, automatically *via* direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware. For clarity NMR spectra are displayed as follows unless this would obscure signals: ^{1}H NMR spectra are displayed between 10 ppm and –0.5 ppm; ^{13}C NMR spectra are displayed between 210 ppm and 0 ppm; ^{19}F NMR spectra are displayed for the full sweep width as acquired. The high resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI) or pneumatically assisted electrospray (pNSI). ESI was performed using a Waters LCT Premier equipped with an ESI source operated in positive ion mode. The software used was MassLynx 4.1, this software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H]. EI was performed using an Autospec Premier Micromass MS technologies. The software used was MassLynx 4.1. pNSI was performed using an Orbitrap XL in positive ion mode. Samples are loop injected into or infused in a stream of H_2O/CH_3OH (1:1 at 50 μL/min) using an appropriate solvent for dissolution of the sample. Nebulization was pneumatically assisted by a flow of N_2 through a sheath around the capillary. CI was performed using a MAT95 magnetic sector instrumentinpositive ionisation mode by "peak matching" with mass resolution between 8000 and 10000 using polyethyleneglycol as reference compound. Commercial reagents were used as supplied, or purified by standard techniques where necessary. Catalysts were purchased from the following suppliers, stored in a dessicator and used without further purification. Iron(III) chloride (CAS: 7705-08-0) was purchased from Acros Organics. Bis(trifluoromethane)sulfonimide lithium salt (CAS: 90076-65-6) was purchased from Sigma-Aldrich. Calcium(II) bis(trifluoromethanesulfonyl)-imide (CAS: 165324-09-4) was purchased from TCI chemicals. **Alcohol substrates** were prepared by the addition of aryl-lithium or Grignard reagents to the corresponding ketones. See SI for full details.

Representative procedures are provided below for the different substrate classes, and different catalysts used. **Supporting Information**: All experimental details and characterization for preparation of alcohol substrates, procedures for Scheme 1, experimental details and characterization data for Schemes 1 to 5, and copies of ^{1}H and ^{13}C NMR spectra.

*Synthesis of 3,3-diaryltetrahydrofurans **9a** and **19b***

4-(3-(4-Chlorophenyl)tetrahydrofuran-3-yl)-2-methylphenol (9a) Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.6 mg, 0.0275 mmol) were added to a solution of tetrahydrofuranol **2a** (99 mg, 0.5 mmol) and 2-methylphenol (270 mg, 2.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/pentane) afforded tetrahydrofuran **9a** (86 mg, 59%) as a white solid. R_f = 0.21 (30% Et_2O/pentane); mp = 137–139 °C; IR (film)/cm^{-1} 3218 (br. OH), 2885, 1739, 1485, 1271, 1216, 1116, 1101, 1053, 1015, 892, 882, 838, 828, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 4 H, 4 × $Ar_{(p\text{-}Cl)}$-CH), 6.99–6.91 (m, 2 H, 2 × $Ar_{(p\text{-}OH)}$-CH), 6.69 (d, J = 8.3 Hz, 1 H, $Ar_{(p\text{-}OH)}$-CH), 5.51 (s, 1 H, OH), 4.35–4.20 (m, 2 H, OCH_2C_q), 4.09–3.93 (m, 2 H, OCH_2CH_2), 2.58 (dt, J = 11.8, 7.4 Hz, 1 H, OCH_2CHH), 2.49 (ddd, J = 12.5, 7.4, 5.7 Hz, 1 H, OCH_2CHH), 2.23 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (Ar-C_q-OH), 144.7 ($Ar_{(p\text{-}Cl)}$-C_q-C_q), 136.9 ($Ar_{(p\text{-}OH)}$-C_q-C_q), 132.0 ($Ar_{(p\text{-}Cl)}$-C_q-Cl), 129.8 ($Ar_{(p\text{-}OH)}$-CH), 128.5 (2 × $Ar_{(p\text{-}Cl)}$-CH), 128.4 (2 × $Ar_{(p\text{-}Cl)}$-CH), 125.6 ($Ar_{(p\text{-}OH)}$-CH), 123.9 (Ar-C_q-CH_3), 114.7 ($Ar_{(p\text{-}OH)}$-CH), 77.2 (OCH_2C_q), 67.2 (OCH_2CH_2), 54.3 (C_q), 38.6 (OCH_2CH_2), 16.0 (CH_3); FTMS (– p NSI) m/z calcd for $C_{17}H_{16}O_2Cl^-$ [M–H]$^-$: 287.0844, Found: 287.0842.

3-(2,4-Dimethoxyphenyl)-3-phenyltetrahydrofuran (19b) Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.6 mg, 0.0275 mmol) were added to a solution of tetrahydrofuran **2b** (82 mg, 0.5 mmol) and 1,3-dimethoxybenzene (0.33 mL, 2.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 50 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/pentane) afforded tetrahydrofuran **19b** (120 mg, 85%) as a white solid. R_f = 0.33 (20% Et_2O/pentane); mp = 110–112 °C; IR (film)/cm^{-1} 2941, 2865, 1607, 1587, 1503, 1257, 1211, 1145, 1063, 1044, 1029, 903, 807, 763, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 1 H, Ar-CH), 7.30–7.22 (m, 4 H, 4 × Ph-CH), 7.19–7.14 (m, 1 H, Ph-CH), 6.55 (dd, *J* = 8.5, 2.5 Hz, 1 H, Ar-CH), 6.42 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 4.77–4.72 (m, 1 H, OC*H*HC$_q$), 4.03–3.95 (m, 2 H, OCH*H*C$_q$ + OC*H*HCH$_2$), 3.91–3.85 (m, 1 H, OCH*H*CH$_2$), 3.84 (s, 3 H, OCH$_3$), 3.52 (s, 3 H, OCH$_3$), 2.65 (dt, *J* = 12.0, 8.6 Hz, 1 H, OCH$_2$C*H*H), 2.51–2.43 (m, 1 H OCH$_2$CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (Ar-*C*$_q$-OCH$_3$), 158.6 (Ar-*C*$_q$-OCH$_3$), 146.3 (Ph-*C*$_q$-C$_q$), 128.1 (Ar-CH), 127.7 (2 × Ph-CH), 126.43 (Ar-*C*$_q$-C$_q$), 126.36 (2 × Ph-CH), 125.6 (Ph-CH), 103.6 (Ar-CH), 99.8 (Ar-CH), 76.8 (O*C*H$_2$C$_q$), 66.4 (O*C*H$_2$CH$_2$), 55.3 (OCH$_3$), 55.2 (OCH$_3$), 53.2 (C$_q$), 38.8 (OCH$_2$*C*H$_2$); FTMS (+ p NSI) m/z calcd for $C_{18}H_{21}O_3^+$ [M+H]$^+$: 285.1485, Found: 285.1486.

*Synthesis of 4,4-diaryltetrahydropyrans **10a** and **10b***

4-(4-(4-Chlorophenyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenol (10a) Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of tetrahydropyran **3a** (106 mg, 0.5 mmol) and 2-methylphenol (270 mg, 2.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O/pentane) afforded tetrahydropyran **10a** (113 mg, 75%) as a white solid. R_f = 0.22 (40% Et_2O/pentane); mp = 170–172 °C; IR (film)/cm^{-1} 3470 (br. OH), 2954, 2860, 1510, 1249, 1236, 1123, 1102, 1090, 1019, 1010, 850, 827, 809, 766, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 2 H, 2 × Ar-CH), 7.23–7.15 (m, 2 H, 2 × Ar-CH), 7.05–6.91 (m, 2 H, 2 × Ar-CH), 6.72 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 5.01 (s, 1 H, OH), 3.86–3.71 (m, 4 H, 2 × CH$_2$O), 2.48–2.31 (m, 4 H, 2 × CH$_2$C$_q$), 2.23 (s, 3 H, CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (Ar-C$_q$-OH), 146.4 (Ar$_{(p\text{-}Cl)}$-*C*$_q$-C$_q$), 138.4 (Ar$_{(p\text{-}OH)}$-*C*$_q$-C$_q$), 131.5 (Ar-*C*$_q$-Cl), 129.5 (Ar$_{(p\text{-}OH)}$-CH), 128.5 (2 × Ar$_{(p\text{-}Cl)}$-CH), 128.2 (2 × Ar$_{(p-Cl)}$-CH), 125.5 (Ar-CH), 123.8 (Ar-*C*$_q$-CH$_3$), 114.9 (Ar$_{(p\text{-}OH)}$-CH), 64.6 (2 × CH$_2$O), 43.1 (C$_q$), 36.9 (2 × C$_q$*C*H$_2$), 16.1 (CH$_3$); FTMS (– p NSI) m/z calcd for $C_{18}H_{18}O_2^-$ [M–H]$^-$: 301.1001, Found: 301.0999.

2-Methyl-4-(4-phenyltetrahydro-2*H*-pyran-4-yl)phenol (10b) Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.6 mg, 0.0275 mmol) were added to a solution of tetrahydropyran **3b** (89 mg, 0.5 mmol) and 2-methylphenol (270 mg, 2.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded tetrahydropyran **10b** (108 mg, 81%) as a white solid. R_f = 0.12 (20% EtOAc/hexane); mp = 159–160 °C; IR (film)/cm^{-1} 3228 (br. OH), 2936, 2874, 1509, 1239, 1093, 823, 749, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 4 H, 4 × Ar-CH), 7.20–7.14 (m, 1 H, Ar-CH), 7.01–6.94 (m, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.86 (s, 1 H, OH), 3.80–3.75 (m, 4 H, 2 × CH$_2$O), 2.45–2.39 (m, 4 H, 2 × CH$_2$C$_q$), 2.21 (s, 3 H, CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (Ar-C$_q$-OH), 147.6 (Ph-*C*$_q$-C$_q$), 138.9 (Ar-*C*$_q$-C$_q$), 129.6 (Ar-CH), 128.4 (2 × Ph-CH), 126.8 (2 × Ph-CH), 125.7 (Ph-CH), 125.5 (Ar-CH), 123.7 (Ar-*C*$_q$-CH$_3$), 114.8 (Ar-CH), 64.8 (2 × CH$_2$O), 43.4 (C$_q$), 36.9 (2 × C$_q$*C*H$_2$), 16.1 (CH$_3$); FTMS (– p NSI) m/z calcd for $C_{18}H_{19}O_2^-$ [M–H]$^-$: 267.1391, Found: 267.1390.

*Synthesis of 3,3-diarylpyrrolidine **12a** and **21b***

Benzyl 3-(4-chlorophenyl)-3-(4-hydroxy-3-methylphenyl)pyrrolidine-1-carboxylate (12a) Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of benzyl 3-(4-chlorophenyl)-3-hydroxypyrrolidine-1-carboxylate **5a** (166 mg, 0.5 mmol) and 2-methylphenol (162 mg, 1.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by dichloromethane (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2 to 5% Et_2O/CH_2Cl_2) afforded benzyl 3-(4-chlorophenyl)-3-(4-hydroxy-3-methylphenyl)pyrrolidine-1-carboxylate **12a** (118 mg, 56%) as a white solid. R_f = 0.43 (5% Et_2O/CH_2Cl_2); mp = 60–63 ºC; IR (film)/cm^{-1} 3304 (br, OH), 2942, 1663 (C=O), 1436, 1251, 1012, 1109, 764, 733, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.29 (m, 5 H, 5 × Ph-H), 7.25–7.21 (d, *J* = 8.6 Hz, 2 H, 2 × Ar-CH), 7.15– 7.09 (m, 2 H, 2 × Ar-CH), 6.91–6.82 (m, 2 H, 2 × Ar-CH), 6.68–6.62 (m, 1 H, Ar-CH), 6.01 and 5.99 (2 × s, 1 H, OH), 5.22 and 5.19 (2 × s, 2 H, OCH$_2$Ph), 4.06–3.91 (m, 2 H, NCH$_2$C(Ar)$_2$), 3.49–3.35 (m, 2 H, NC*H*$_2$CH$_2$), 2.56–2.38 (m, 2 H, NCH$_2$C*H*$_2$), 2.18 and 2.17 (2 × s, 3 H, CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 and 154.9 (C=O), 152.9 (Ar-C$_q$-OH), 144.2 and 144.1 (Ar-C$_q$), 136.64 and 136.62 (Ar-C$_q$), 136.3 and 136.2 (Ar-C$_q$), 132.2 and 132.1 (Ar-C$_q$-Cl), 129.4 and 129.3 (Ar-CH), 128.7, 128,6, 128.52, 128.50, 128.4, 128.1, 128.02, 127.99, 127.9 (8 × Ar-CH), 127.7 (C$_{Ar}$), 124.9 and 124.8 (Ar-CH), 124.2 (Ar-*C*$_q$-CH$_3$), 114.73 and 114.66 (Ar-CH), 67.2 and 67.0 (OCH$_2$Ph), 55.94 and 55.90 (NCH$_2$C(Ar)$_2$), 52.8 and 52.0 (C$_q$(Ar)$_2$), 44.7 and 44.3 (NCH$_2$CH$_2$), 37.3 and 36.6 (NCH$_2$*C*H$_2$), 16.1 (CH$_3$); HRMS (ESI$^+$) *m/z* Calcd for $C_{25}H_{25}NO_3{}^{35}Cl$ [M+H] 422.1523; Found 422.1507.

Benzyl 3-(2,4-dimethoxyphenyl)-3-phenylpyrrolidine-1-carboxylate (21b) Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of benzyl 3-hydroxy-3-phenylpyrrolidine-1-carboxylate **5b** (149 mg, 0.5 mmol) and 1,3-dimethoxybenzene (0.20 mL, 1.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by dichloromethane (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (10% to 20% EtOAc/hexane) afforded benzyl 3-(2,4-dimethoxyphenyl)-3-phenylpyrrolidine-1-carboxylate **21b** (151 mg, 72%) as an amorphous solid. R_f = 0.20 (20% EtOAc/hexane); IR (film)/cm^{-1} 2955, 2884, 1697 (C=O carbamate), 1610, 1583, 1505, 1447, 1412, 1358, 1342, 1208, 1160, 1141, 1108, 1081, 1031, 731, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.30 (m, 6 H, 6 × Ar-CH), 7.28–7.12 (m, 5 H, 5 × Ar-CH), 6.54–6.50 (m, 1 H, Ar-CH), 6.39 (t, *J* = 2.3 Hz, 1 H, Ar-CH), 5.30–5.19 (m, 2 H, OCH$_2$Ph), 4.65 (d, *J* = 11.8 Hz, 0.5 H, NC*H*HC(Ar)$_2$), 4.48 (d, *J* = 11.8 Hz, 0.4 H, NC*H*HC(Ar)$_2$), 3.82 (s, 3 H, OCH$_3$), 3.76–3.66 (m, 1 H, NCH*H*C(Ar)$_2$), 3.58–3.46 (m, 4 H, NC*H*HCH$_2$ and OCH$_3$), 3.34–3.20 (m, 1 H, NCH*H*CH$_2$), 2.68–2.55 (m, 1 H, NCH$_2$C*H*H), 2.47–2.37 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (Ar-C$_q$-OMe), 158.5 and 158.4 (Ar-C$_q$-OMe), 154.7 (C=O carbamate), 145.4 (Ar-C$_q$), 145.1 (Ar-C$_q$), 137.2 and 137.1 (Ar-C$_q$), 128.4, 128.3, 127.8, 127.7, 127.6, 127.3, 127.31, 126.28, 126.2, 126.0, 125.70, 125.67 (11 × Ar-CH), 103.6 and 103.5 (Ar-CH), 100.0 and 99.7 (Ar-CH), 66.6 and 66.5 (OCH$_2$Ph), 55.2, 55.1, 55.0 (NCH$_2$C(Ar)$_2$ and 2 × OCH$_3$), 51.7 and 50.8 (C$_q$(Ar)$_2$), 44.1 and 43.6 (NCH$_2$CH$_2$), 37.6 and 36.6 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calcd for $C_{26}H_{28}NO_4$ [M+H] 418.2018; Found 418.2039.

*Synthesis of 4,4-diarylpiperidines **13a** and **13c***

Benzyl 4-(4-chlorophenyl)-4-(4-hydroxy-3-methylphenyl)piperidine-1-carboxylate (13a) Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of benzyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate **6a** (173 mg, 0.5 mmol) and 2-methylphenol (162 mg, 1.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 50 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by dichloromethane (30 mL). The layers were separated and the aqueous portion was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2 to 5% to 10% Et_2O/CH_2Cl_2) afforded benzyl 4-(4-chlorophenyl)-4-(4-hydroxy-3-methylphenyl)-piperidine-1-carboxylate **13a** (111 mg, 51%) as a white solid. R_f = 0.32 (5% Et_2O/CH_2Cl_2); mp = 75–81 ºC; IR (film)/cm^{-1} 3322 (br, OH), 2951, 1668, 1438, 1248, 906, 727, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5 H, 5 × Ar-CH), 7.25 (d, *J* = 8.6 Hz, 2 H, 2 × Ar-CH), 7.14 (d, *J* = 8.6 Hz, 2 H, 2 × Ar-CH), 6.96–6.89 (m, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.13 (s, 2 H, OCH_2Ph), 4.71 (s, 1 H, OH), 3.64–3.46 (m, 4 H, 2 × NCH_2CH$_2$), 2.40–2.19 (m, 7 H, 2 × NCH$_2$CH_2 and CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C=O), 152.6 (Ar-C_q-OH), 145.8 (Ar-C_q-CH_3), 136.8 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 131.6 (Ar-C_q-Cl), 129.4 (Ar-CH), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.2 (2 × Ar-CH), 128.0 (Ar-CH), 127.8 (2 × Ar-CH), 125.3 (Ar-CH), 124.2 (Ar-C_q-C_q), 114.9 (Ar-CH), 67.2 (OCH_2Ph), 43.7 (C_q), 40.9 (2 × NCH_2), 36.0 and 35.7 (2 × CH_2), 16.2 (CH_3); HRMS (ESI$^+$) *m/z* Calcd for $C_{26}H_{27}NO_3{}^{35}Cl$ [M+H] 436.1679; Found 436.1681.

Benzyl 4-(3-hydroxy-4-methylphenyl)-4-(4-methoxyphenyl) piperidine-1-carboxylate (13c) Calcium(II) bis(trifluoromethane-sulfonimide) (7.5 mg, 12.5 µmol) and tetrabutylammonium hexafluorophosphate (4.8 mg, 12.5 µmol) were added to a solution of piperidinol **6c** (85 mg, 0.25 mmol) and 2-methylphenol (81 mg, 0.75 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded piperidine **13c** (45 mg, 40%) as a white solid. R_f = 0.41 (30% EtOAc/hexane); mp = 93 °C; IR (film)/cm^{-1} 3329 (br. OH), 2932, 1667 (C=O), 1608, 1509, 1438, 1351, 1245, 1181, 1107, 1029, 816, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5 H, 5 × Ar-CH), 7.16–7.12 (m, 2 H, 2 × Ar-CH), 6.95 (d, *J* = 2.3 Hz, 1 H, Ar-CH), 6.89 (dd, *J* = 8.4, 2.3 Hz, 1 H, Ar-CH), 6.85–6.81 (m, 2 H, 2 × Ar-CH), 6.69 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.36 (s, 1 H, OH), 5.14 (s, 2 H, CH_2-Ph), 3.78 (s, 3 H, OCH_3), 3.57–3.54 (m, 4 H, CH_2NCH_2), 2.31 (s, 4 H, CH_2CCH_2), 2.20 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (Ar-C_q-OCH_3), 155.5 (C=O), 152.1 (Ar-C_q-OH), 139.0 (Ar-C_q-CH_3), 138.5 (Ar-C_q-C_q), 136.8 (Ar-C_q-CH_2), 129.5 (Ar-CH), 128.4 (2 × Ar-CH), 127.92 (Ar-CH), 127.88 (2 × Ar-CH), 127.8 (2 × Ar-CH), 125.4 (Ar-CH), 123.8 (Ar-C_q-C_q), 114.8 (Ar-CH), 113.8 (2 × Ar-CH), 67.1 (CH_2-Ph), 55.2 (OCH_3), 43.5 (C_q), 41.1 (2 × CH_2), 36.3 and 36.1 (2 × CH_2), 16.2 (CH_3); HRMS (ESI) *m/z* Calcd for $C_{27}H_{30}NO_4$ [M+H]: 432.2175; Found: 432.2166.

*Synthesis of diarylcyclobutanes **14a** and **14c***

4-(1-(4-Chlorophenyl)cyclobutyl)-2-methylphenol (14a) Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of cyclobutanol **7a** (91 mg, 0.5 mmol) and *o*-cresol (155 µL, 1.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by dichloromethane (30 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (5% Et_2O/pentane) afforded cyclobutane **14a** (109 mg, 80%) as a colorless oil. R_f = 0.23 (5% Et_2O/pentane); IR (film)/cm^{-1} 3384 (br, OH), 2974, 2940, 1490, 1263, 1185, 1114, 1010, 816, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 4 H, 4 × Ar-CH), 7.02–6.99 (m, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 4.60 (s, 1 H, OH), 2.76–2.59 (m, 4 H, CH_2CH$_2$CH_2), 2.22 (s, 3 H, CH_3), 1.96 (dddd, *J* = 15.2, 8.2, 6.9, 4.1 Hz, 2 H, CH$_2$CH_2CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (Ar-C_q-OH), 148.8 (Ar-C_q-CH_3), 141.4 (Ar-C_q-C_q), 131.0 (Ar-C_q-Cl), 128.8 (Ar-CH), 128.3 (2 × Ar-CH), 127.5 (2 × Ar-CH), 124.6 (Ar-CH), 123.5 (Ar-C_q-C_q), 114.6 (Ar-CH), 50.1 (C_q), 35.0 ($CH_2CH_2CH_2$), 16.5 (CH_3), 16.0 ($CH_2CH_2CH_2$); HRMS (ESI$^-$) *m/z* Calcd for $C_{34}H_{31}O_2Cl_2$ [2M-H]: 541.1701; Found: 541.1710.

4-(1-(4-Methoxyphenyl)cyclobutyl)-2-methylphenol (14c) Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of cyclobutanol **7c** (89 mg, 1.0 mmol) and *o*-cresol (155 µL, 1.5 mmol) in dichloromethane (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by dichloromethane (30 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (5 to 10 % Et_2O/pentane) afforded cyclobutane **14c** (92 mg, 72%) as a white solid. R_f = 0.10 (5% Et_2O/pentane); mp = 89–92 °C; IR (film)/cm^{-1} 3345 (br, OH), 3205, 2937, 1612, 1505, 1461, 1410, 1360, 1237, 1176, 1125, 1019, 812; ^{1}H NMR (400 MHz, $CDCl_3$) 7.25–7.20 (m, 2 H, 2 × Ar-CH), 7.05–6.99 (m, 2 H, 2× Ar-CH), 6.86–6.81 (m, 2 H, 2 × Ar-CH), 6.69 (d, *J* = 8.1 Hz, 1 H, Ar-CH), 4.62 (s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 2.72–2.63 (m, 4 H, CH_2CH$_2$CH_2), 2.22 (s, 3 H, CH_3), 1.96 (tt, *J* = 8.7, 6.9 Hz, 2 H, CH$_2$CH_2CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (Ar-C_q-OCH_3), 151.4 (Ar-C_q-OH), 142.5 (Ar-C_q-CH_3), 142.4 (Ar-C_q-C_q), 128.8 (Ar-CH), 127.1 (2 × Ar-CH), 124.6 (Ar-CH), 123.3 (Ar-C_q-C_q), 114.5 (Ar-CH), 113.5 (2 × Ar-CH), 55.2 (OCH_3), 49.9 (C_q), 35.2 ($CH_2CH_2CH_2$), 16.5 (CH_3), 16.0 ($CH_2CH_2CH_2$); HRMS (EI$^+$) *m/z* Calcd for $C_{18}H_{20}O_2$ [M]: 268.1463; Found: 268.1458.

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[33] Such reactivity differences suggest a related stabilizing effect invoking a lone pair of electrons is not likely to be operative with the oxetane or azetidine examples.

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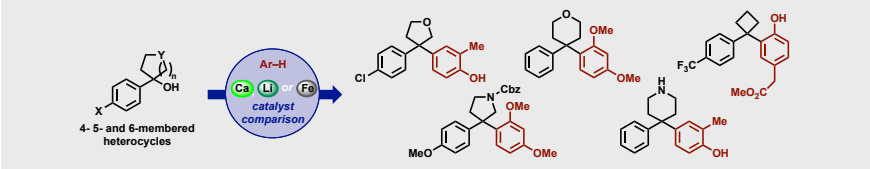

A systematic comparison of Lewis acid catalysts [Ca(II), Li(I) and Fe(III)] is presented for catalytic Friedel–Crafts reactions using alcohols on 4-, 5-, and 6-membered oxygen and nitrogen heterocycles and cyclobutanes, forming *gem*-diaryl quaternary centers.

Heterocycles

*R. A. Croft, M. A. J. Dubois, A. J. Boddy, C. Denis, A. Lazaridou, A. S. Voisin-Chiret, R. Bureau, C. Choi, J. J. Mousseau, J. A. Bull**

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