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Diastereoselective Benzylic Arylation of Tetralins

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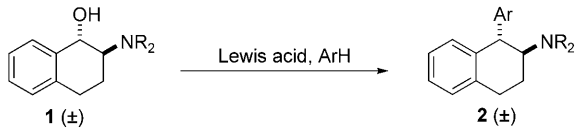
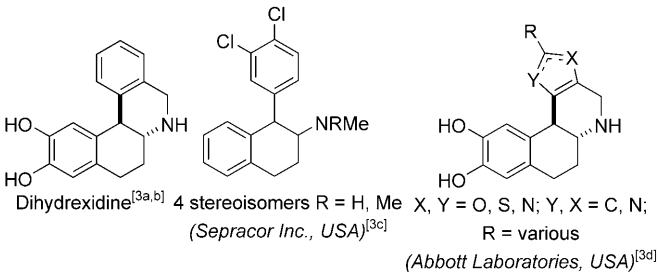
In recent years, significant research efforts have been focused on benzylic arylation chemistry utilising Friedel–Crafts alkylation protocols.[1,2] Advances in this area include the use of milder reaction conditions and the use of inexpensive and relatively non-toxic catalysts. In addition to these new protocols, the field of diastereoselective Friedel–Crafts chemistry has also begun to emerge.[2] Of note is research conducted by Bach and colleagues, who observed highly diastereoselective Friedel–Crafts alkylation reactions involving 1-aryl-1-alkanols.[2d] They report that the diastereoselectivity of the reaction proved to be dependent on the functional group that was present at the 2-position. Herein, we report intermolecular, *trans*-selective Friedel–Crafts protocols for the benzylic arylation of tetralin systems **1** (Scheme 1). The high diastereoselectivity is proposed to be



Scheme 1. *trans*-Selective benzylic arylation of tetralin systems.

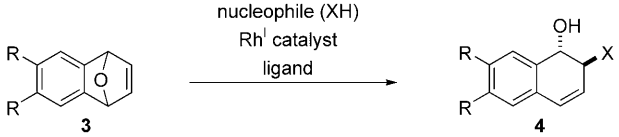
induced by the presence of a coordinating, nitrogen-containing group at the 2-position, rather than purely steric effects. The tetralin core is featured in many pharmaceutically relevant compounds, thus a method of accessing this core in a selective fashion is warranted (Scheme 2).[3]



Scheme 2. Relevant compounds featuring an aryl-substituent at the benzylic position on the tetralin core.

Our group has had a longstanding interest in the ring-opening reactions of oxabicyclic alkenes.[4] The rhodium(I)-catalysed ring-opening of *meso*-oxabicyclic alkenes **3** with various nucleophiles selectively affords the *trans*-products **4** (Scheme 3). This reaction may be performed in a racemic fashion using 1,1′-bis(diphenylphosphino)ferrocene (DPPF) as the ligand or enantioselectively (up to 99% *ee*) using the Josiphos-type ligand, (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine (PPF-P*t*Bu$_2$). Using this methodology various tetralins were prepared and, following hydrogenation of the alkene functionality, were used as substrates in an intermolecular Friedel–Crafts alkylation study.

In the first instance, this study was undertaken using tetralin **5a** as substrate and toluene (20 equivalents) as the aromatic nucleophile (Table 1). Among the Brønsted and Lewis acids investigated (Table 1, entries 1–5), $AlCl_3$ gave the most promising result. Under these conditions (Table 1, entry 2), only the *para*-substituted, *trans*-diastereomer **7aa** was observed, as determined by ^{1}H NMR analysis of the crude re-



Scheme 3. General scheme for the *trans*-selective rhodium(I)-catalyzed ring-opening of *meso* oxabicyclic alkenes.

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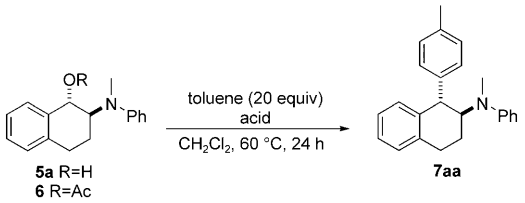
Table 1. Optimisation of the conditions for the Friedel–Crafts reaction of tetralin **5a** with toluene.[a]



5a R=H
6 R=Ac

7aa

Entry	Substrate	Acid	Acid equiv	Yield [%][b]
1	**5a**	$FeCl_3$	1	traces
2	**5a**	$AlCl_3$	1	36[c]
3	**5a**	$AuCl_3$	1	0
4	**5a**	*p*TsOH	1	0
5	**5a**	CSA	1	0
6	**6**	$AlCl_3$	1	20
7	**5a**	$AlCl_3$	1.2	34
8	**5a**	$AlCl_3$	2	61 (52)[d]
9[e]	**5a**	$AlCl_3$	2	85[d]

[a] Reaction mixtures were stirred in a sealed tube, heated to 60 °C for 24 h. [b] Determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, in the presence of an internal standard. [c] 40 % conversion. [d] Yield of isolated product. [e] Reaction was performed at a concentration of 0.3 M.

action mixture. However, the reaction proceeded to only 40 % conversion. Optimisation of this reaction involved the use of two equivalents of $AlCl_3$ (Table 1, entry 8) and an increase in the concentration of the reaction from 0.1 M to 0.3 M (Table 1, entry 9).

The apparent requirement for an additional equivalent of $AlCl_3$ may be to counteract coordination of the acid with the amine, or alternatively because the eliminated water effectively consumes one equivalent of the acid. Nonetheless, using these conditions, the desired *trans*-diastereomer was isolated in 85 % yield. Single-crystal X-ray analysis of this compound confirmed the *trans*-arrangement of substituents (Figure 1). This impressive intermolecular, *trans*-selective Friedel–Crafts result complements the observations made by us and others in the intramolecular benzylic arylation of tetralin systems using Friedel–Crafts chemistry, in which the *cis*-isomer is formed exclusively.[3a,5]

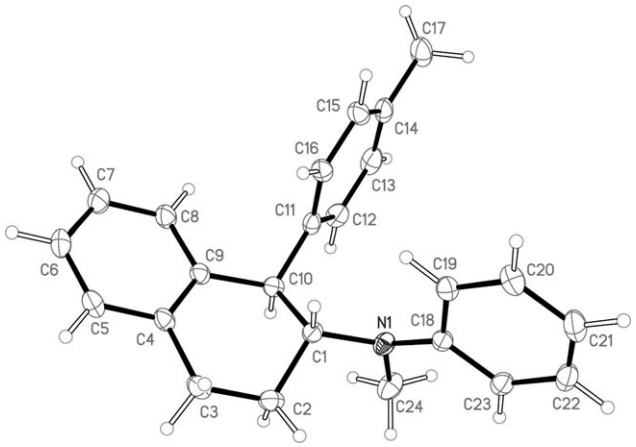


Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **7aa**.

In an effort to explore the scope of this reaction, the Friedel–Crafts reactions of toluene with several other nitrogen-based tetralin substrates **5b**–**5j** were investigated by using the optimised conditions (Table 2). In all cases, the desired *para*-substituted, *trans*-diastereomers **7ba**–**7ja** were the only compounds observed, and good to excellent yields were obtained. Of particular mention, is that the free amine substrate **5f** gave the *trans*-isomer **7fa** in 84 % yield (Table 2, entry 6). Thus, regardless of the steric and/or electronic influences within substrates **5a**–**5f** only the *trans*-isomers were obtained.

Table 2. Friedel–Crafts reaction involving toluene and various nitrogen-based tetralin substrates.

5a-5j

7aa-7ja

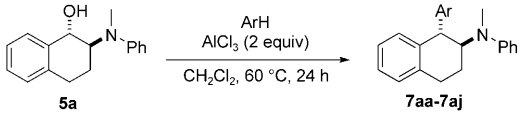
Entry	Substrate	R^1, R^2	X	Product	Yield [%][a]
1	**5a**	H, H	NMePh	**7aa**	85
2	**5b**	H, H	NEt_2	**7ba**	75
3	**5c**	H, H	NHHex	**7ca**	74
4	**5d**	H, H	NHPh	**7da**	61
5	**5e**	H, H	NPhth	**7ea**	60
6	**5f**	H, H	NH_2	**7fa**	84
7[b]	**5g**	OMe, H	NMePh	**7ga**	22[c]
8	**5h**	F, H	NMePh	**7ha**	80
9	**5i**	Br, H	NMePh	**7ia**	91
10	**5j**	Br, Me	NMePh	**7ja**	92

[a] Yield of isolated product. [b] Reaction was performed at a concentration of 0.1 M. [c] Yield at full conversion.

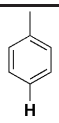
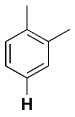
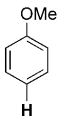
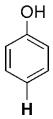
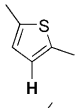
Substrates bearing substituents on the aryl ring were also investigated (Table 2, entries 7–10). While the reaction involving the dimethoxy derivative **5g** (Table 2, entry 7) afforded the desired *trans*-product **7ga** in only 22 % yield, the halogen-substituted substrates **5h**–**5j** gave the desired products **7ha**–**7ja** in excellent yields (Table 2, entries 8–10). In the investigations by Bach and co-workers, no reaction was observed unless the substrate 1-aryl-1-alkanols were substituted on the aryl-ring with appropriately positioned methoxy or alkyl groups.[2d] These substituents are proposed to provide stabilisation effects during carbocation formation. For the tetralin substrates there appear to be no problems in forming the intermediate carbocation species, as even the fluorine-substituted compounds afforded the desired *trans*-product in high yield.

The scope of the aryl nucleophile employed in the Friedel–Crafts reaction was then investigated by using tetralin substrate **5a** (Table 3). In many instances, the number of equivalents of nucleophile was reduced from 20 to 5 with no effect on the yield. In general, several aromatic and hetero-

Table 3. Friedel–Crafts reaction involving various nucleophiles and tetralin substrate **5a**.



5a **7aa-7aj**

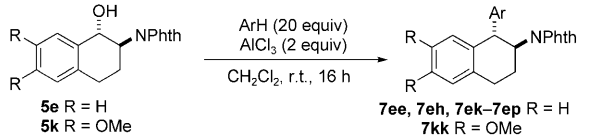
Entry	ArH	ArH equiv	Product	Yield [%][a]
1		20	**7aa**	85
2		5		81[b]
3		5	**7ab**	74
4[c]		20	**7ac**	74 (4:0:96)[d]
5		5		75[b]
6		20	**7ad**	56 (27:0:73)[d]
7		5		50 (30:0:70)[d]
8		5	**7ae**	69 (88:12)[e]
9		5	**7af**	73
10		5	**7ag**	82[f]
11		5	**7ah**	83 (49:7:44)[g]
12		5	**7ai**	61
13		5	**7aj**	51 (54:46)[e]

[a] Yield of isolated product, ratio in parentheses refers to regioisomers and is as determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, in the presence of an internal standard. [c] Reaction was performed at a concentration of 0.1 M. [d] *o*/*m*/*p* ratio, yield refers to major regioisomer. [e] 2-/3-Regioisomers. [f] Corrected for the purity of the sample. [g] 2-/4-/5-Regioisomers.

aromatic nucleophiles proved to be compatible with the reaction conditions and afforded the desired *trans*-products in good yields. In addition, thiophene derivatives reacted smoothly (Table 3, entries 8–11), although in some instances, multiple regioisomers were observed. Indole and *N*-methylpyrole also proved to be suitable (Table 3, entries 12 and 13), however, in these cases incomplete conversion was observed. No reaction of the substrate **5a** with furan derivatives occurred under these conditions.

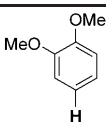
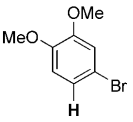
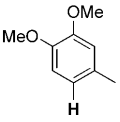
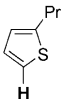
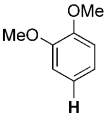
For the benzylic arylation of the phthalimide-tetralin substrate **5e**, a second, milder protocol involving room temperature reaction conditions was developed (Table 4).

Table 4. Friedel–Crafts reaction involving various aryl-nucleophiles and tetralin substrates **5e** and **5k**.



5e R = H
5k R = OMe

7ee, 7eh, 7ek–7ep R = H
7kk R = OMe

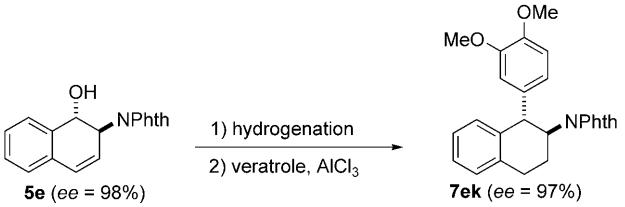
Entry	Substrate	ArH	Product	Yield [%][a]
1	**5e**		**7ek**	92
2[b]	**5e**			94
3[b,c]	**5e**			95
4	**5e**		**7el**	77
5[b,d]	**5e**			76
6[b]	**5e**		**7em**	72
7	**5e**		**7en**	79
8	**5e**		**7ee**	82 (95:5)[e]
9	**5e**		**7eh**	78 (83:17)[f]
10[g]	**5e**		**7eo**	91
11[g,h]	**5e**		**7ep**	78 (82:18)[e]
12[b,h]	**5k**		**7kk**	80

[a] Yield of isolated product. [b] 1.1 equivalents of ArH were present. [c] One equivalent of $AlCl_3$ was present. [d] Scale of the reaction was increased from 0.341 mmol to 1.02 mmol. [e] Ratio in parentheses refers to 2-/3-regioisomers and is as determined by ^{1}H NMR analysis of the isolated sample. [f] Ratio in parentheses refers to 2-/5-regioisomers and is as determined by ^{1}H NMR analysis of the isolated sample. [g] Five equivalents of ArH were present. [h] Reaction was performed at a concentration of 0.1 M.

Single regioisomers were generally isolated and all contained a *trans*-arrangement of substituents. In addition, only 1.1 equivalents of the highly activated veratrole-type nucleophiles was required and the scale of the reaction could be increased three-fold without having a detrimental effect on the reaction outcome (Table 4, entry 5). Furthermore, under these conditions, substrates that had proven to be problem-

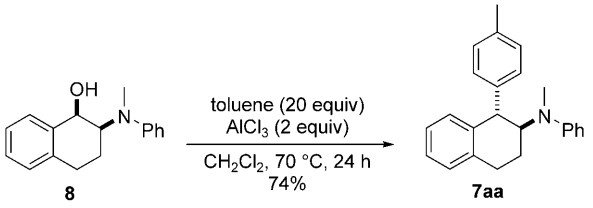
atic under the previous protocol, such as a dimethoxy derivative **5k** (Table 4, entry 12) were reactive giving the desired *trans*-product in excellent yield. In addition, this protocol allows reactions involving more sensitive nucleophiles, such as furan (Table 4, entry 7) and greater regioselectivity was observed. It is worth noting that while two equivalents of $AlCl_3$ were used in this study, it was subsequently shown that the reaction to produce tetralin **7ek** was also successful in the presence of one equivalent of $AlCl_3$ (Table 4, entry 3). This result supports the notion that two equivalents of the Lewis acid are generally required to counteract coordination of the acid to amino groups present at the 2-position of the tetralin substrates.

Following the development of successful protocols for the *trans*-selective benzylic arylation of racemic tetralin systems, the Friedel–Crafts reaction conditions were applied to the phthalimide-tetralin substrate **5e**, which was prepared in an enantioselective fashion (*ee* of the rhodium(I)-catalysed ring-opening product determined to be 98%). Thus, following hydrogenation of the alkene functionality, and reaction with veratrole under the optimised Friedel–Crafts conditions, the enantiomeric excess of the product tetralin **7ek** was determined to be 97% (Scheme 4). Therefore, the two-step reaction sequence does not result in a loss in the enantiomeric purity of the sample.



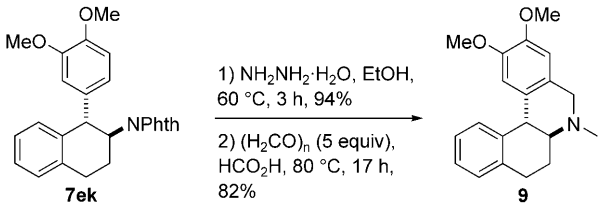
Scheme 4. Preparation of tetralin **7ek** in high enantiopurity.

To probe the mechanism of this *trans*-selective Friedel–Crafts reaction, the *cis*-tetralin substrate **8** was prepared and subjected to the reaction conditions with toluene as nucleophile (Scheme 5). As expected, the *trans*-product **7aa** was isolated, thus supporting the idea of an intermediate benzylic carbocation species. While there is no doubt that steric factors would favour the formation of the *trans*-product, the exclusive formation of the *trans*-compounds, especially in the case of the non-congested free amine substrate suggests that additional factors may be involved (Table 2, entry 6). In such instances, we propose that the nitrogen atom on the adjacent carbon atom to the in situ generated carbocation species may coordinate to this site, shielding this face from nucleophilic attack, and therefore resulting in the formation of the *trans*-product. Further investigations into the mechanism of this reaction are underway.



Scheme 5. Reaction of *cis*-tetralin **8** with toluene.

To further demonstrate the utility of these *trans*-selective Friedel–Crafts procedures, compound **7ek** was treated with hydrazine to afford the primary amine, which upon treatment with paraformaldehyde in formic acid, underwent a one-pot Pictet–Spengler/Eschweiler–Clarke methylation reaction to give the tetracyclic tertiary amine compound **9** (Scheme 6). The core of this compound bears similarity to the pharmaceutically relevant compounds shown in Scheme 2.



Scheme 6. Synthesis of tetracyclic amine **9**.

In summary, we have developed Friedel–Crafts protocols for the intermolecular, *trans*-selective benzylic arylation of tetralin systems. Attractive features of these protocols are the broad substrate scope, ease, and scalability of the reactions. Furthermore, the use of enantiopure substrates allows the preparation of the *trans*-aryl-substituted tetralins in high *ee*. Further investigations into the mechanism of this reaction and expansion on the scope of the reaction are underway.

Acknowledgements

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Keywords: alkylation · benzylic alcohols · carbocations · diastereoselectivity · electrophilic aromatic substitution

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