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Accessing bridged bicyclic compounds or *meta* carbon-functionalized anilines from the dearomatization of anilines†

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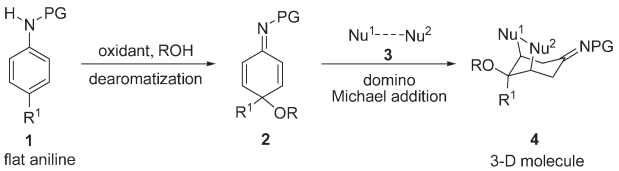
The oxidative dearomatization of anilines was combined with a domino Michael addition, providing a series of nitrogen-containing bridged bicyclic compounds in moderate to excellent yields. The bridged bicyclic compound could be converted into the corresponding *meta* carbon-functionalized aniline derivative *via* a quinine-catalyzed tandem retro-oxa-Michael addition–aromatization reaction.

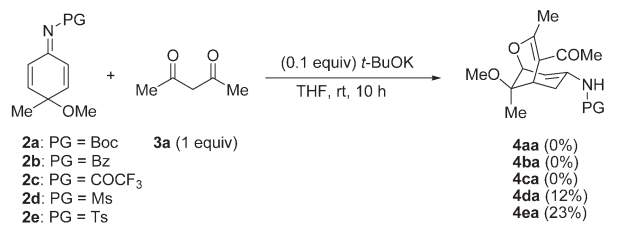
The rapid and economic construction of architecturally complex molecules from simple starting materials is a crucial aspect in organic synthesis. The dearomatization of aromatic compounds, a powerful tool in organic synthesis, has been intensively explored and utilized by organic chemists in complex syntheses.[1] Due to the significance of aromatic amines as attractive starting materials in organic synthesis, some of our recent efforts have led to the development of new reactions based on the dearomatization of aniline derivatives.[2] Utilising this work, we are interested in exploring the possibility of building 3-D molecules from flat anilines through a domino reaction[3,4] (Scheme 1). The resulting bridged bicyclic compound could be a potential precursor to many biologically active compounds, such as gelsemine and huperzine A.[5]

We initially evaluated the reaction between pentane-2,4-dione **3a** and cyclohexadienimines[6] **2a–e** (Scheme 2). The nitrogen protecting group played a significant role in the transformation. No reaction was observed when an *N*-Boc, *N*-Bz or *N*-$COCF_3$ protected substrate was used. Ms and Ts groups proved to be suitable nitrogen protecting groups for the double Michael addition. The desired bridged bicyclic compounds **4da** and **4ea** were obtained in 12% and 23% yields, respectively. The structure of compound **4ea** was confirmed by single-crystal diffraction analysis (Fig. 1, see ESI† for details).[7] With this promising lead in hand, the effects of various solvents, temperatures and ratios of reagents were examined (see ESI†). The yield of compound **4ea** was improved to 98% when the reaction was conducted in methanol, with 3 equiv. of pentane-2,4-dione and 0.5 equiv. of CH_3ONa at room temperature, for 4 h. When the reaction was conducted on a 5 mmol scale, compound **4ea** was obtained in an 87% yield.



Scheme 1 Building 3-D molecules from flat anilines.

After optimising the reaction conditions, the scope of this domino Michael addition was explored, and the results are summarized in Table 1. Since some of the cyclohexadienimines were sensitive to hydrolysis, the crude dearomatization reaction mixtures were directly used in the domino Michael addition. The C-4 substitution of cyclohexadienimines could be an alkyl, phenyl or methoxy group. The 4-alkoxy group could also be an ethoxy group. When the C-3 or C-2 positions of cyclohexadienimine were blocked by a methyl or a phenyl group, the reaction still proceeded



Scheme 2 Reaction between pentane-2,4-dione **3a** and cyclohexadienimines **2a–e**.

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† Electronic supplementary information (ESI) available: Evaluation of reaction conditions, experimental procedures, characterization data, copies of ^1H NMR and ^{13}C NMR spectra of new compounds. CCDC reference number 891422. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra23224g

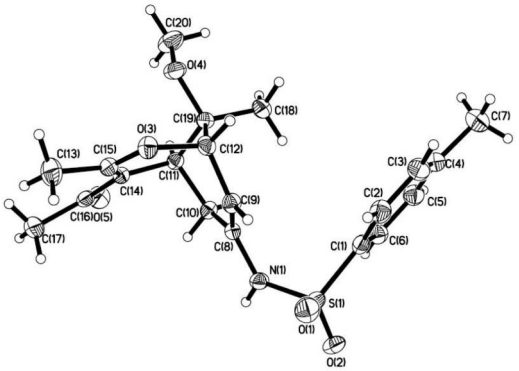


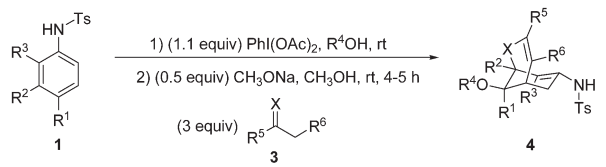
Fig. 1 X-ray diffraction structure of compound **4ea**.

smoothly, and provided product **4ka** or **4la** in 83% and 63% yields, respectively. With respect to other bis-nucleophiles, methyl or ethyl acetoacetate and 1-(methylsulfonyl)propan-2-one were also suitable reaction partners. When methyl 3-aminobut-2-enoate **3e** was used,[8] bridged aza-bicyclic products **4ee** and **4he** were formed in moderate yields.

When *N*-Ts-4-methyl-2-(2-phenylethynyl)benzenamine **1m** was employed, the resulting bridged bicyclic compound **4ma** could be converted to the 4,5,6,7-tetrahydro-1*H*-indole derivative **5ma** *via* a silver-catalyzed cyclization (Scheme 3).

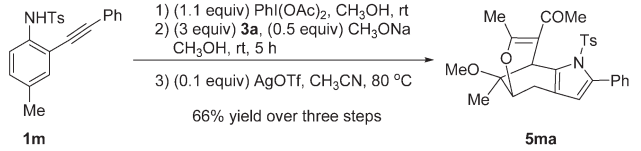
As an electron-donating substituent, the amine group normally directs incoming substituents to the *ortho* and *para* positions.

Table 1 Construction of bridged bicyclic compounds *via* dearomatization and domino Michael addition[a]



Entry	R^1	R^2	R^3	R^4	R^5	R^6	X	Yield of 4 (%)
1	Me	H	H	Me	Me	COMe	O	**4ea** (91)
2	Et	H	H	Me	Me	COMe	O	**4fa** (50)
3	*n*-Bu	H	H	Me	Me	COMe	O	**4ga** (62)
4	Ph	H	H	Me	Me	COMe	O	**4ha** (81)
5	OMe	H	H	Me	Me	COMe	O	**4ia** (80)
6	Me	H	H	Et	Me	COMe	O	**4ja** (61)
7	Me	Me	H	Me	Me	COMe	O	**4ka** (83)
8	Me	H	Ph	Me	Me	COMe	O	**4la** (63)
9	Me	H	H	Me	Me	COOMe	O	**4eb** (88)
10	Ph	H	H	Me	Me	COOMe	O	**4hb** (91)
11	Me	H	H	Et	Me	COOMe	O	**4jb** (62)
12	Me	Me	H	Me	Me	COOMe	O	**4kb** (61)
13	Me	H	Ph	Me	Me	COOMe	O	**4lb** (70)
14	Me	H	H	Me	Me	COOEt	O	**4ec** (79)
15	Me	H	H	Me	Me	SO_2Me	O	**4ed** (71)
16	Me	H	H	Me	Me	COOMe	NH	**4ee** (47)
17	Ph	H	H	Me	Me	COOMe	NH	**4he** (51)
18	Ph	H	H	Me	CF_3	COOEt	O	**4ef** (0)
19	Ph	H	H	Me	OMe	COOMe	O	**4eg** (0)

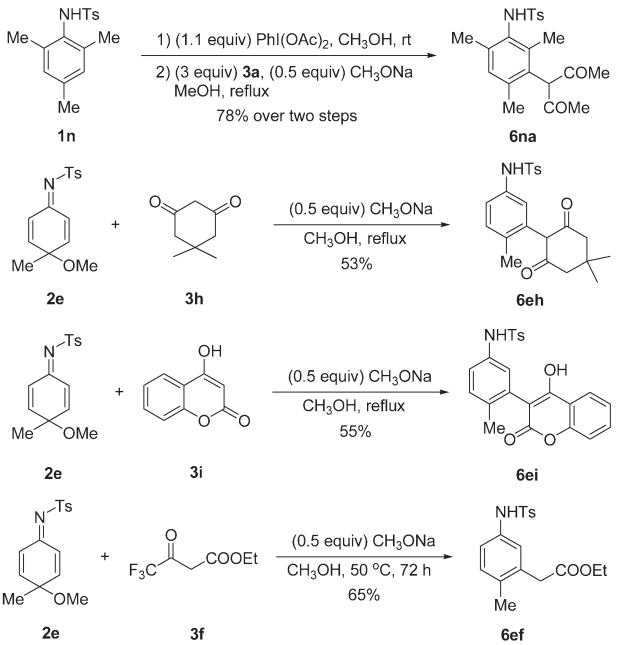
[a] Isolated yield based on compound **1**.



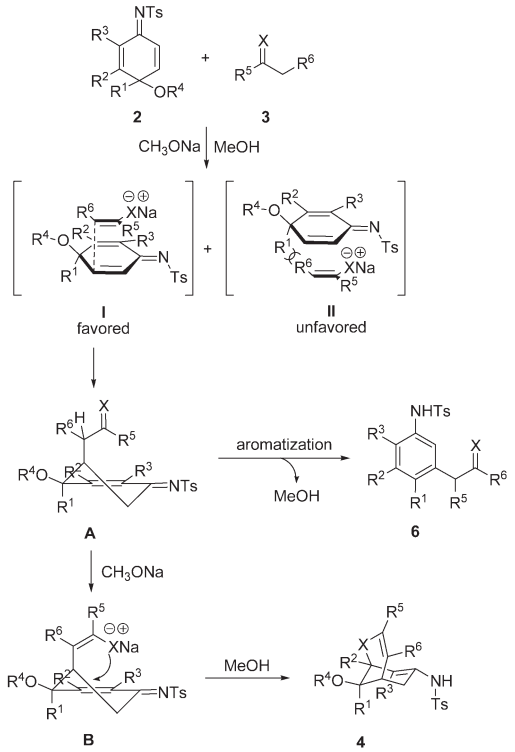
Scheme 3 Formation of the 4,5,6,7-tetrahydro-1*H*-indole derivative **5ma**.

Meta substitution of aromatic amines by carbon functional groups remains a challenge in organic synthesis.[9] It is noteworthy that the reaction of 2,4,6-trimethylbenzenamine, which was sluggish at room temperature, gave rise to a *meta* carbon-functionalized aniline derivative **6na** in a 78% yield when the reaction was conducted under reflux. *Meta* functionalization of *p*-toluidine was also observed when 5,5-dimethylcyclohexane-1,3-dione (**3h**), 4-hydroxy-2*H*-chromen-2-one (**3i**), or 4,4,4-trifluoro-3-oxobutanoate (**3f**) was used as the nucleophile (Scheme 4).

A plausible reaction pathway is depicted in Scheme 5. The domino sequence is initiated by the 1,4-conjugate addition of the bis-nucleophile[10] to the cyclohexadienimine at the less hindered position. Because of the steric hindrance of the R^1 group (R^1 = alkyl or phenyl), this reaction is diastereoselective from the face of the OR^4 group leading to the Michael adduct **A**. In the presence of a base, the intermediate **B** undergoes an intramolecular 1,4-conjugate addition to form the bridged bicyclic compound **4**. When the C-2 and C-6 positions of cyclohexadienimine were blocked by methyl groups, or when 5,5-dimethylcyclohexane-1,3-dione or 4- hydroxy-2*H*-chromen-2-one was used, the second Michael addition failed due to the steric hindrance effect or the constrained conformation of the cyclic bis-nucleophiles.[11] In the case of ethyl 4,4,4-trifluoro-3-oxobutanoate, the strong electron-



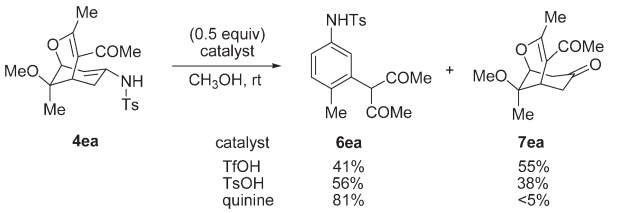
Scheme 4 Formation of 3-substituted anilines.



Scheme 5 A plausible reaction pathway.

withdrawing properties of the CF_3 group (R^5) reduced the nucleophilicity of the neighbouring carbonyl oxygen and suppressed the second Michael addition. After elimination of a trifluoroacetate group[12] and subsequent aromatization, compound **6ef** was formed.

To investigate the possibility of converting the bridged bicyclic compound to the corresponding *meta* carbon-functionalized aniline derivative, compound **4ea** was treated with CH_3ONa in methanol under reflux. The formation of compound **6ea** was not detected, and a 96% yield of compound **4ea** was recovered after 1 h. Since compound **4ea** was stable under basic conditions, various Lewis acids or Brønsted acids were examined as catalysts to promote the retro-oxa-Michael addition–aromatization sequence, but the results were not satisfactory. For example, in the presence of 0.5 equiv. of trifluoromethanesulfonic acid (TfOH) or 4-methylbenzenesulfonic acid (TsOH), conversion of compound **4ea** was observed, but the reaction gave rise to two major products. One was the desired compound **6ea**, and the other was identified as the bridged bicyclic compound **7ea**, which was assumed to be generated from the hydrolysis of the enamine moiety. After countless failures, we found that quinine was an effective catalyst to promote the retro-oxa-Michael addition–aromatization reaction. In the presence of 0.5 equiv. of quinine, the bridged bicyclic compound **4ea** was converted to the *meta* carbon-functionalized aniline derivative **6ea** in an 81% yield (Scheme 6).



Scheme 6 Aromatization of bridged bicyclic compound **4ea**, forming the *meta* carbon-functionalized aniline derivative **6ea**.

Conclusions

In summary, we have explored a route to build nitrogen-containing bridged bicyclic compounds from simple anilines *via* an oxidative dearomatization and a domino Michael addition. An advantage of this methodology is that *meta* carbon-functionalized aniline derivatives can be prepared with significant regiocontrol. Further studies on the synthetic applications of this methodology are currently under investigation at our laboratory.

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