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C–H Activation

Regio- and Diastereoselective and Enantiospecific Metal-Free C(sp^3)–H Arylation: Facile Access to Optically Active 5-Aryl 2,5-Disubstituted Pyrrolidines

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Abstract: Optically active 5-aryl 2,5-disubstituted pyrrolidines are the principal structural moiety of many bioactive compounds including natural products and catalysts for asymmetric synthesis. A highly regio- and diastereoselective and enantiospecific method for direct C–H arylation of aliphatic amine has been developed. Structurally diverse enantiopure arylated pyrrolidines were synthesized from commercially available starting materials, through a single-step three-component reaction under metal- and oxidant-free conditions. Furthermore, the complex analogous structure of CCK antagonist RP 66803 and angiotensin-converting enzyme inhibitors was easily constructed using the synthesized arylated pyrrolidine derivative. Detailed theoretical calculations (M06-2X/TZVPP/SMD//M06-2X/6-31+G(d,p) level) were also carried to investigate the mechanism and high level of stereocontrol involved in this direct sp^3 C–H arylation reaction. Preference for a given regio- and stereoselectivity in the arylated product can be explained through elucidation of the mechanism for dehydration, generating azomethine ylide, and for the final re-aromatization step. The calculated energies reveals that the re-aromatization step is essentially rate determining, accompanying an activation barrier of $\Delta^{\ddagger}G^{S}_{L} = 25.6$ kcal mol^{-1}.

Introduction

Arylated pyrrolidine serves as the key structural motif of many natural and synthetic functional molecules.[1] For some relevant examples, they are present in different bioactive natural products like prolinalin B,[1d] (−)-codonopsinine,[1e] and radicamine B[1f,g] (Figure 1). Moreover, many medicinally important synthetic molecules are built on arylated pyrrolidine. Enantiopure 5-arylproline derivative is the core unit of CCK antagonist (RP 66803),[1h] angiotensin-converting enzyme (ACE) inhibitor[1i,j] and Schramm's C-azanucleoside[1k] having potential trypanosomal activity. Other than pharmacological applications, enantioenriched arylated pyrrolidine based molecules have important value in organic synthesis. They are either used directly or in the presence of metal catalyst to promote asymmetric reactions.[2] The obvious widespread application of enantioenriched arylated pyrrolidine derivatives, in both medicinal chemistry and organic synthesis, demands the development of novel and applicable methods for their preparation. Various methods have been reported for the synthesis of the arylated pyrrolidines.[3–5] However, strategies for syntheses of these molecules in enantiomerically pure form are limited. Chiral auxiliary-based strategies were mainly employed in this regard.[6] In addition, a few enantioselective strategies were also applied.[7] However, primarily multistep *N*-cycloalkylation strategies involving chiral

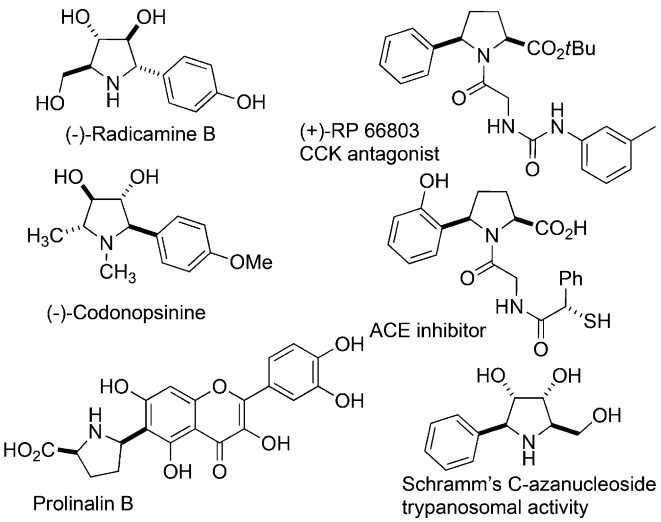

Figure 1. 5-Aryl 2,5-disubstituted pyrrolidines in bioactive molecules.

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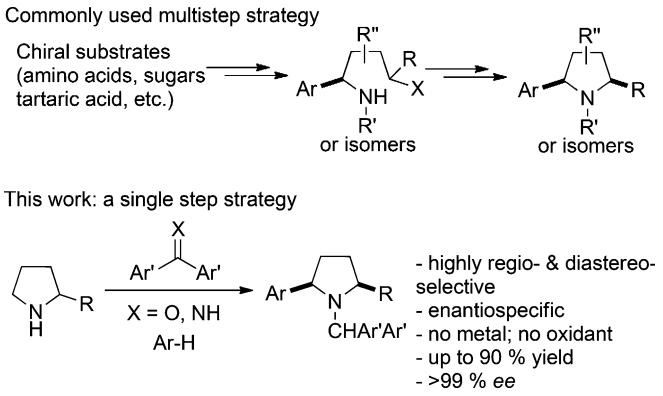
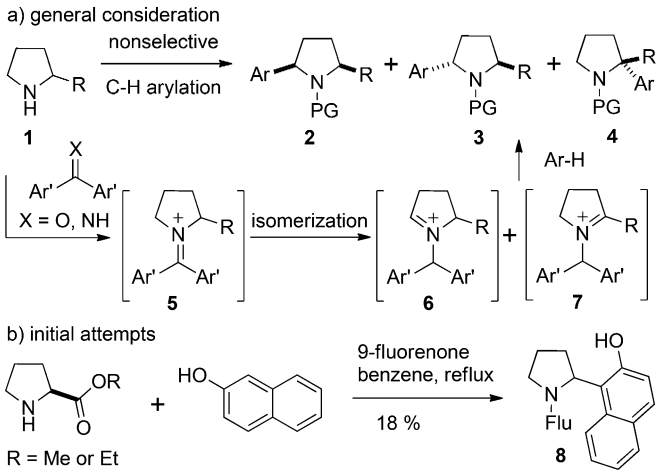


Scheme 1. Syntheses of optically active 5-aryl 2,5-disubstituted pyrrolidines.



Scheme 2. a) Challenges and opportunity of direct C–H arylation of substituted pyrrolidine; b) arylation of L-proline methyl ester.

amines were adopted for syntheses of enantioenriched 2,5-disubstituted pyrrolidines (Scheme 1).[8,2e] A diastereoselective carboxylation[9] involving stoichiometric amount of chiral reagent and a diastereoselective Heck arylation[10] were developed to obtain the 2,5-disubstituted pyrrolidine, albeit with moderate yield and selectivity. An asymmetric hydrogenation strategy was also employed for reduction of substituted pyrrole under high pressure of hydrogen.[11] The main drawback of known protocols, with a view to their practical application, originates from their multistep reaction sequences, often with moderate diastereoselectivities. We report herein the first example of metal- and oxidant-free highly regio- and diastereoselective and enantiospecific direct sp^3 C–H arylation to access enantioenriched 2,5-disubstituted pyrrolidine derivatives (Scheme 1).

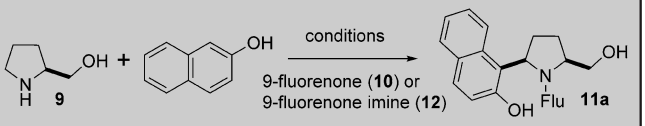
During our ongoing investigations into direct functionalization of aliphatic amines,[12] we developed a method for direct C–H arylation of pyrrolidine by a simple three-component reaction under metal- and oxidant-free conditions.[5l] Almost at the same time, a similar report was published by Seidel and co-workers.[5m] However, no report on stereoselective C–H arylation of substituted pyrrolidine to access enantiopure 2,5-disubstituted pyrrolidine was reported to date. The possibility to obtain enantioenriched 2,5-disubstituted pyrrolidines by direct C–H functionalization of commercially available starting materials will be of particular interest in the context of finding new bioactive compound and chiral scaffold for asymmetric catalysis. However, readily available enantiopure proline loses its chirality due to decarboxylation during the arylation reaction.[5h–j]

Experimental Results and Discussion

General notes on direct C–H arylation reaction

Generally, during direct C–H arylation of substituted *N*-heterocycle **1**, reaction should overcome regio- and diastereoselectivity issues to avoid forming a mixture of diastereoisomers **2**, **3** and **4** (Scheme 2a). The use of enantiopure starting material, aiming for enantioenriched product, put further challenges due to the possibility of racemization that may allow formation

Table 1. Optimization of the reaction condition.[a]



Entry	Activator	Solvent, Temp.	Time	Yield [%][b]
1	**10**	THF, reflux	48 h	37
2	**10**	THF, reflux	78 h	65
3[c]	**10**	benzene, reflux	66 h	59
4	**10**	toluene, μw, 150 °C	40 min	46
5	**12**	THF, reflux	66 h	56
6	**12**	benzene, reflux	72 h	71
7	**12**	toluene, μw, 150 °C	30 min	53
8	**12**	toluene, μw, 150 °C	40 min	65
9	**12**	xylene, μw, 170 °C	40 min	31
10	**12**	CH_3CN, μw, 100 °C	40 min	20
11	**12**	DCM, μw, 60 °C	40 min	trace
12	**12**	EtOH, μw, 100 °C	40 min	trace
13	**12**	benzene, μw, 100 °C	40 min	12

[a] Reactions were carried out with prolinol **9** (0.3 mmol), 2-naphthol (0.25 mmol), and 9-fluorenone **10** (0.3 mmol) or its imine derivative **12**. [b] Yields of isolated product. [c] Prolinol (3.0 equiv) was used in excess.

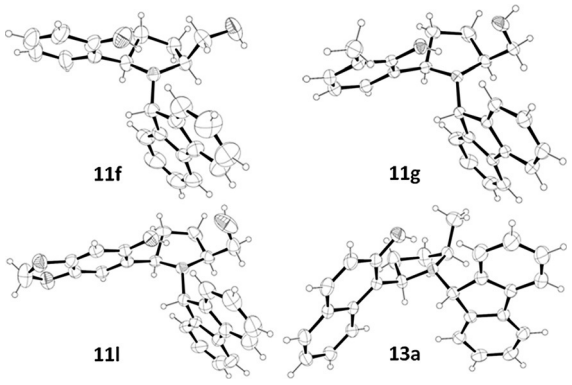


Figure 2. ORTEP representations of representative compounds **11 f**, **11 g**, **11 l** and **13 a** showing relative *syn* stereochemistry. Thermal ellipsoids are set at 30% probability.

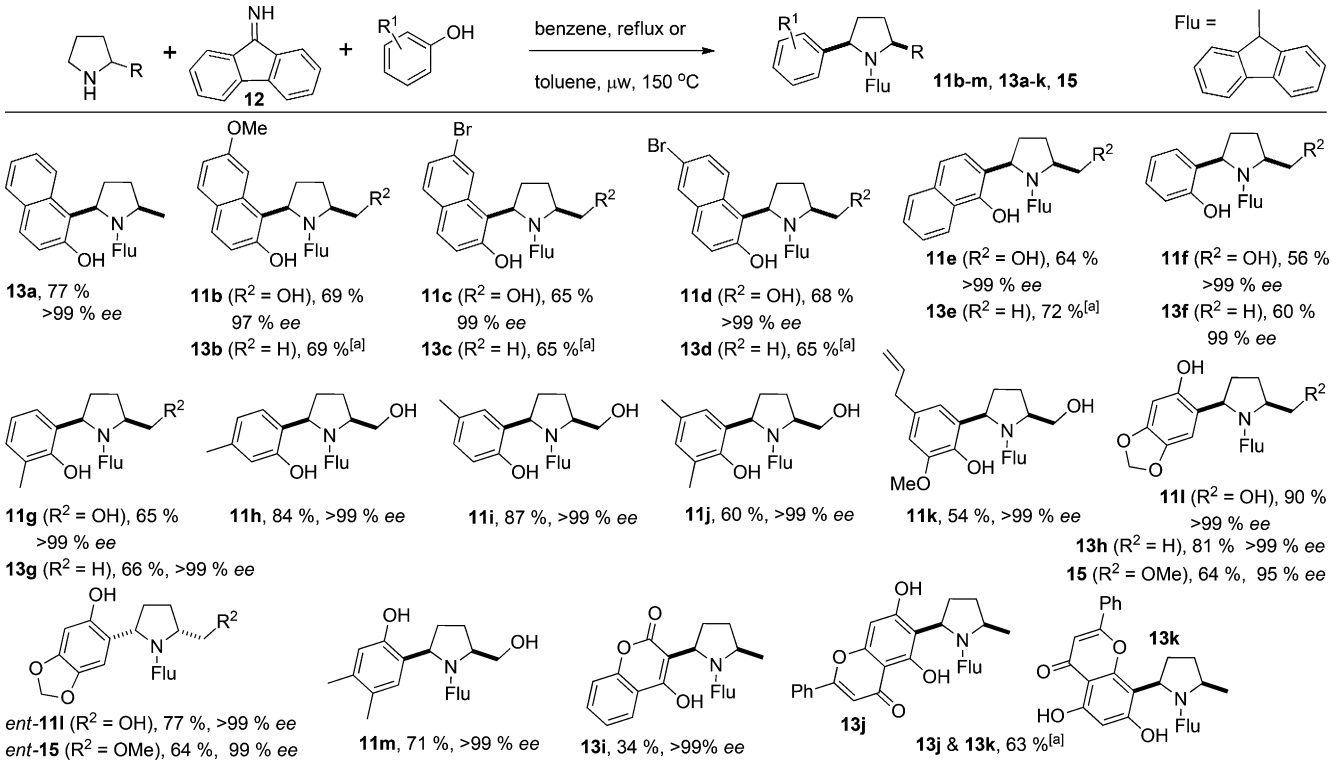
of a mixture of six isomers. Preferences for the formation of the less-substituted enamine, to avoid the allylic strain that exists in its more substituted isomer, have been well documented.[13] Therefore, we anticipated that the isomerization of the initially formed iminium ion **5** could be preferentially drawn towards **6** due to the unfavorable allylic strain in its regioisomer **7**. Thus the selective formation of **6** will solve the regioselectivity issue, as well as the racemization problem. The remaining facial selectivity can be controlled by tuning the nature of Ar, R, and CHAr′Ar′ (PG) to afford one isomer selectively.[14] It was thought that the ester derivative of proline may be used to avoid decarboxylation during the direct C–H arylation reaction. However, decarboxylation was found even in a reaction of L-proline methyl or ethyl ester, providing arylated pyrrolidine **8** (Scheme 2b).

Evaluation of reaction conditions

We started our investigation with the attempt to functionalize commercially available enantiomerically pure (*S*)-prolinol **9**. To start with, enantioenriched prolinol reacted with 9-fluorenone **10** in tetrahydrofuran under reflux condition in the presence of 2-naphthol as a potential nucleophile. After 48 h, the desired product **11a** was isolated in 37% yield as a single diastereoisomer (Table 1, entry 1). The relative *syn* stereochemistry was assigned in analogy of the stereochemistry observed from the single crystal X-ray structures of **11f**, **11g**, and **11l** (Figure 2). To our delight, we also found that the chiral center of starting prolinol **9** was retained to provide **11a** with >99% enantiomeric excess. This encouraging finding led us to investigate the reaction further to improve the yield. Higher reaction time (78 h) increased the chemical yield to 65% (Table 1, entry 2). Efforts were then continued to decrease the reaction time. We anticipated that the reaction time could be reduced by promoting the reaction of secondary amine and carbonyl compound. Therefore, we employed 9-fluorenone imine **12** instead of 9-fluorenone to facilitate the reaction more effectively. A maximum yield of 71% of the desired product was obtained after 72 h (Table 1, entry 6). Moreover, a 53% yield was obtained in 30 min when the reaction was carried out at 150 °C in toluene under microwave irradiation (Table 1, entry 7). At the same time, the reaction was highly stereoselective, providing **11a** as the sole isomer with unaltered enantiopurity. The yield was further increased to 65% by increasing the reaction time to 40 min (Table 1, entry 8). The effects of varying other reaction conditions, such as solvent, temperature, and carbonyl compound (activator), were also examined. A trace amount of the product was obtained when using protic and low-boiling solvents (Table 1, entry 11 and 12). Other activators, such as benzophenone, anthrone, and anthraquinone, which are analogous to 9-fluorenone, failed to produce the corresponding C–H-arylated compounds. Thus the reactions using 9-fluorenone imine in benzene under reflux and in toluene at 150 °C for 40 min under microwave irradiation were found to be superior for this C–H arylation process.

Substrate scope of the direct C–H arylation reaction

We then utilized the optimized reaction conditions to investigate the substrate scope. Different electron-rich aromatic com-



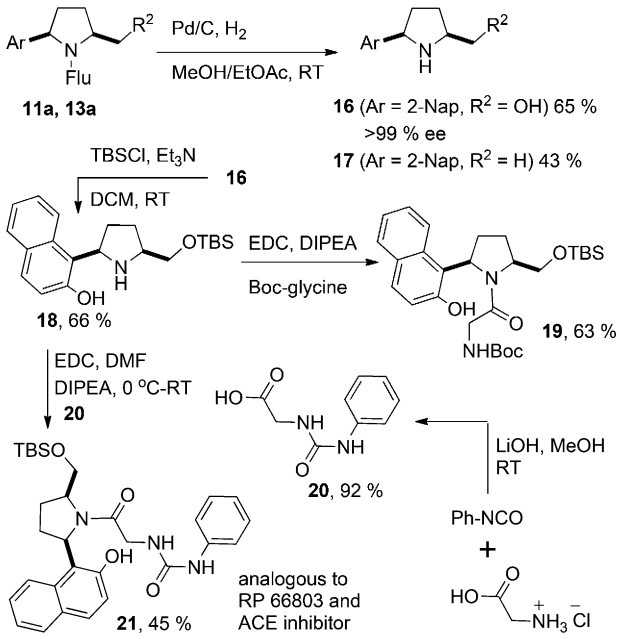
Scheme 3. Substrate scope of arylation reaction; [a] reactions were carried out with racemic amine.

pounds were used for the direct C–H functionalization of prolinol and 2-methyl pyrrolidine (Scheme 3). Naphthols and their derivatives reacted smoothly, providing different 2,5-disubstituted pyrrolidine derivatives (**11b–e** and **13a–e**) with very good yields and excellent stereoselectivities. Aside from naphthols, phenol derivatives and 4-hydroxycoumarin were also employed as the effective nucleophiles producing C–H-functionalized derivatives (**11f–m**, **15**, and **13f–k**). Functional groups that are sensitive towards transition metal- and oxidant-mediated reaction were well tolerated in this reaction. Two regioisomeric products **13j** and **13k** were isolated when chrysin was used as the nucleophile. The best yield (90%) of arylated pyrrolidine derivative **11l** was obtained when a highly oxygenated phenol derivative, sesamol (**14**), was employed as the nucleophile. Similarly, arylated amine **15** was obtained with 65% yield and >99% *ee* through arylation of 2-methoxymethyl pyrrolidine.

In all cases, the products were isolated as the single diastereoisomer. The relative *syn* orientation of the aryl and alkyl groups in **11f**, **11g**, **11l** and **13a** were confirmed from their corresponding molecular structures obtained via the single crystal X-ray diffraction analysis (Figure 2).[15] During the C–H arylation of enantiopure (*S*)-pyrrolidine methanol and its derivatives, arylated compounds were found by HPLC analysis to have excellent enantiopurities. Optically pure arylated compounds (*ent*-**11l** and *ent*-**15**) were also obtained from (*R*)-pyrrolidine methanol and its *O*-methylated derivatives. Analogous retention of the chiral center occurred during the arylation of enantioenriched (*R*)-2-methylpyrrolidine, providing 5-aryl 2-methylpyrrolidines with excellent enantiopurities (>99%). However, indole derivatives, the most widely used nucleophilic aromatic substrates, were unable to provide acceptable yields of the corresponding C–H arylated compounds under these conditions, indicating that the phenolic OH plays an important role in the reaction.

Synthesis and derivatization of chiral amines

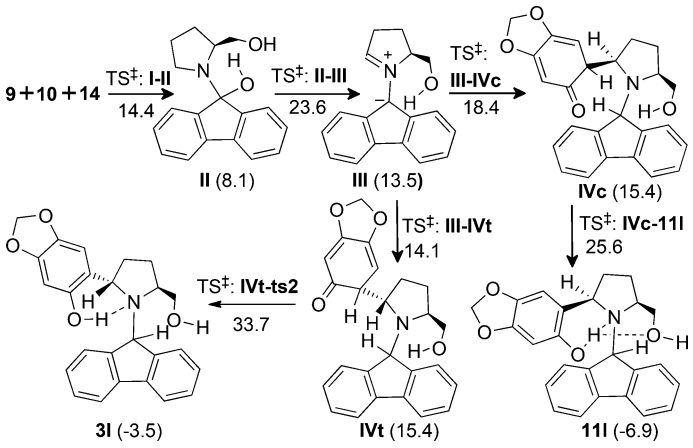
Enantiopure *N*-fluorenyl 2,5-disubstituted pyrrolidine derivatives, which were obtained by this method, can be used directly as the chiral ligand in metal-catalyzed asymmetric reactions.[2] Further modification to form the free amine would open an important avenue in finding new bioactive compounds and chiral scaffolds for asymmetric catalysis. For *N*-defluorenylation, the pyrrolidine derivative **11a** was subjected to hydrogenolysis conditions to give the 5-aryl prolinol **16** with 65% yield and with retention of enantiomeric excess (>99% *ee*; Scheme 4). Similarly, compound **13a** provided the corresponding secondary amine **17**. The corresponding phenyl derivative of **16** was prepared by a linear 10-step synthetic sequence in the context of the synthesis of RP 66803.[8e] The primary hydroxy group was selectively silylated under standard conditions to provide silyl ether **18** (66%). The enantioenriched 5-arylated prolinol **18** then reacted efficiently with Boc-protected glycine to afford the dipeptide **19** (63%). Similarly, urea derivative **20**, prepared from glycine in 92% yield, was coupled with **18** to provide dipeptide **21**, which structurally resembles biologically important dipeptides such as RP 66803 and ACE inhibitors.



Scheme 4. Syntheses of chiral amines and their synthetic applications.

Computational Results and Discussion

DFT calculations were performed at M06-2X/TZVPP/SMD//M06-2X/6-31+G(d,p) level of theory (see computational details in the Supporting Information) to illustrate the origin of regio- and stereoselectivity in the reaction of (*S*)-prolinol **9** with sesamol **14** in the presence of 9-fluorenone **10**. Three possible isomeric product, **11l**, **3l**, and **4l**, corresponding to **2**, **3** and **4** respectively, can be formed in this C–H arylation reaction



Scheme 5. Proposed mechanism of the overall reaction. The respective energy terms (in kcal mol^{-1}) below the arrows and in parenthesis are activation barrier ($\Delta^{\ddagger}G_L^S$) and relative free energy (ΔG_L^S) with respect to the starting materials at M06-2X/TZVPP/SMD//M06-2X/6-31+G(d,p) level.

(Scheme 2a and Scheme S1 in the Supporting Information).[16] The reaction pathway (Scheme 5) obtained from the calculated results consists of following two steps: I) nucleophilic attack of **9** on **10** followed by dehydration to generate azomethine ylide (**III**) and II) nucleophilic attack of **14** at the iminium ion center (C^2, Figure 3) to deliver intermediates **IVt/IVc**, which can finally re-aromatize to furnish the desired product.

Step I

In the initial step, nucleophilic addition of N^1–H^1 of **9** to the carbonyl group, C^3=O^2 of **10** via a four-membered cyclic transition state (**9**–**10** in Figure 3) requires high activation barrier of 37.0 kcal mol^{-1}, which is similar to the value of 32.5 kcal mol^{-1} previously reported by Yu and co-workers in their investigation of the formation of *N*-alkyl pyrroles.[17] However, this step is accelerated in presence of sesamol, since the accompanying six member transition state, **I**–**II** encounters a low activation barrier ($\Delta^{\neq}G_L^S = 14.1$ kcal mol^{-1}, Figure 3 and Scheme 5). The resulting hemiaminal **II** then undergoes dehydration to generate ylide **III**. The dehydration process requires the protonation of **II**, giving rise to an iminium ion **II-OH** (see the Supporting Information, Figure S1). Unfortunately this step is highly endergonic by 58.7 kcal mol^{-1}, since the ionic species formed are destabilized in a nonpolar toluene environment. However, sesamol-assisted dehydration in a concerted manner requires accessible activation barrier ($\Delta^{\neq}G_L^S = 23.6$ kcal mol^{-1}) for the transition state **II**–**III** (Figure 3). The geometry of the transition state reveals that sesamol donates a proton to the OH group at C^3 to liberate water with concomitant acceptance of a proton from the C^2 center. The water molecule has already been decoordinated from C^3 and the N^1–C^3 bond (Figure 3) is

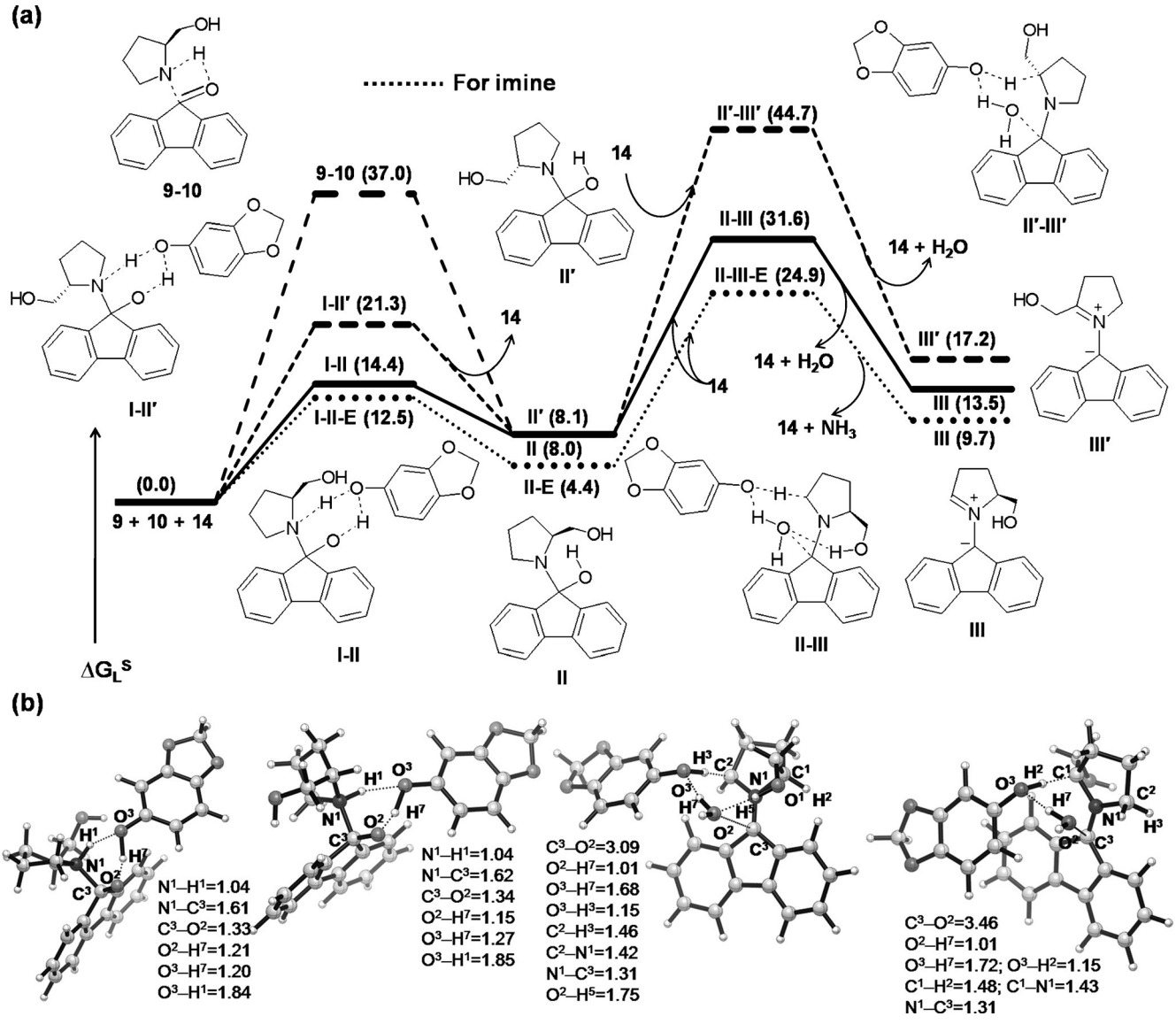


Figure 3. a) Energy profile [in kcal mol^{-1} at M06-2X/TZVPP/SMD//M06/6-31+G(d,p) level] for the nucleophilic attack of **9** on **10** followed by dehydration in the presence of **14**. Square dotted and solid lines represent the formation pathways of ylides **III** and **III'**, respectively. The round dotted line shows the energy profile for 9-fluorenone imine **12**; b) optimized geometries of transition states at M06-2X/6-31+G(d,p) level involve in this step.

shortened by 0.15 Å (**II**→**II**–**III**) in the transition-state geometry. The resulting ylide **III** is less stable than the reactants by 13.5 kcal mol^{-1}, indicating its enhanced reactivity in the presence of a nucleophile. A concerted pathway that generates regioisomer **III**′ from **II** is highly unlikely, since the H^2 at C^1 is *anti* to the O^2H^7 group at C^3 (Figure 3). Therefore, another isomer of **II**, that is, **II**′, is necessary to undergo the sesamol-assisted dehydration process to furnish isomer **III**′. Unsurprisingly, the transformation **II**′→**III**′ has a high activation barrier of 36.6 kcal mol^{-1} (see the Supporting Information, Figure S1) because, unlike **II**→**III** the H^2 atom is less positive than H^3 in **II**/**II**′(q_{H^2/H^3} = 0.12/0.21 *e*; see the Supporting Information, Table S1). Since formation of the intermediate **III**′ requires comparatively high energy, we have not considered the subsequent steps leading to regioisomer **4 l** in this study (see the Supporting Information, Scheme S1).[16] Encouraged by the experimental findings, we performed an additional investigation using the imine analogue **12** as an alternative activating agent. Employing **12**, we report a low lying pathway accessible for the formation of **III** (round dotted line in Figure 3). This result explains the experimental finding of faster rate in the presence of **12**.

Step II

The next step could proceed via protonation followed by nucleophilic attack of sesamol at the zwitterion **III**. NBO (Natural Bond Orbital) results indicate that C^3 is more electron rich than C^2 of the pyrrolidine fragment in ylide **III** (q_{C^3/C^2} = −0.029/0.077 *e*; see the Supporting Information, Table S1). This electronic arrangement is further supported by the Kohn–Sham (KS) frontier orbitals (see the Supporting Information, Figure S3). The HOMO of **III** is mostly contributed by C^3 (C^3: 38%, C^2: 18%) whereas the LUMO of **III** is centered at C^2 (C^2: 45%, N^1: 17%). Protonation at C^3 of **III** leads to a more unstable ionic species, **III-P**. The endergonicity (ΔG^S_L = 43.3 kcal mol^{-1}) is due to the formation of an ionic species that is destabilized in nonpolar toluene medium. The reactive **III-P** can immediately combine with the sesamolate (RO^-) fragment giving rise to either of the stereoisomeric intermediates **IVc** or **IVt** (Figure 4a).Therefore, the favorable route may follow the initial protonation at C^3 and subsequent nucleophilic attack at C^2 in a single step, concerted fashion (Figure 4). Depending on the approach of sesamol, formation of two isomeric intermediates **IVc** and **IVt** can be envisaged. **III-IVc** and **III-IVt** represents the respective transition states accompanying energy barriers of 18.4 and 14.2 kcal mol^{-1} respectively. In both cases, the imaginary frequencies correspond to the combined mode of proton transfer from O^3 to C^3 and concomitant C^4–C^2 bond formation (Figure 4b).

Finally, re-aromatizations of **IVc** and **IVt** generate the respective C–H arylated products **11 l** and **3 l** (Figure 5 and Figure S3 in the Supporting Information). Several pathways for re-aroma-

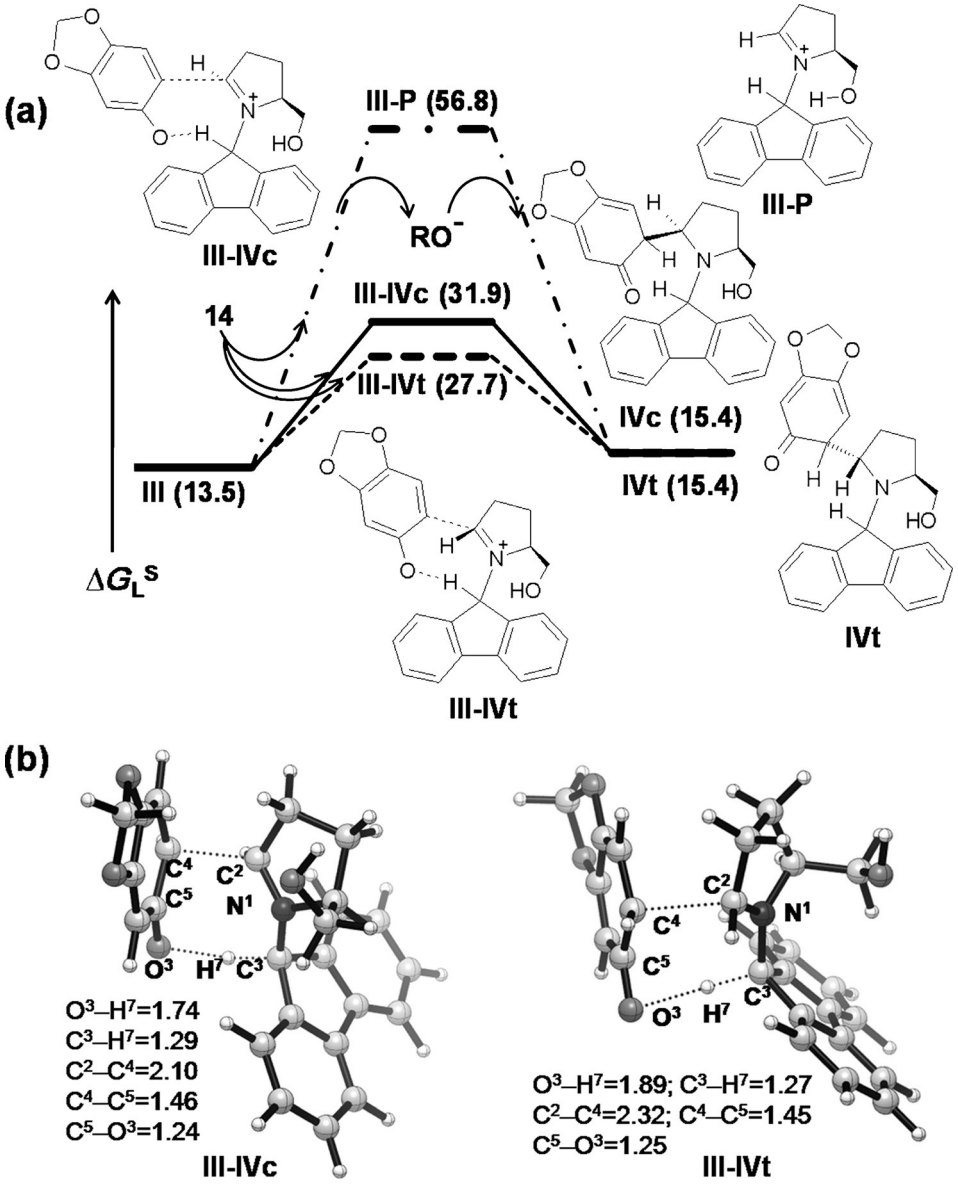


Figure 4. a) Energy profile for nucleophilic addition of **14** to **III**. Solid and square dotted lines are for concerted pathways of **IVc** and **IVt** formation, respectively and dashed dotted line shows stepwise protonation followed by nucleophilic attack; b) optimized geometries of transition states involved in this step. For energy and other conventions, refer to Figure 3.

tization have been investigated; the results are collected in Figures 5 and S3. In the first case, proton transfer from C^4 to O^3 following keto-enol tautomerism requires high-energy transition states, [$\Delta^{\neq}G_L^S$(**IVc-ts**/**IVt-ts**) = 54.2/54.1 kcal mol^{-1}; Figure 5, –•–•] since such 1,3-hydride shift is known to be forbidden.[18] Secondly, any possibility of an intermolecular proton exchange from external sesamol can also be ruled out due to high energy barriers [$\Delta^{\neq}G_L^S$(**IVc-ts1**/**IVt-ts1**) = 39.6/36.8 kcal mol^{-1}; Figure 5, •••••]. Interestingly, in a similar 1,3-H shift where the H^6 is shared between C^4 and N^1 in the transition states, the activation barriers for this step are reduced to moderate energy values compared to previous pathways[$\Delta^{\neq}G_L^S$(**IVc-ts2**/**IVt-ts2**) = 28.1/33.7 kcal mol^{-1}; Figure 5, -----]. The imaginary mode for these two transition states involves the proton transfer from the C^4 to the N^1 center (Figure 5 b). Most importantly, these transition states transform into the respective products **11 l** and **3 l** during IRC (Intrinsic Reaction Coordinate) optimizations. However, it is interesting to note that even though the two transition states **IVc-ts2** and **IVt-ts2** show similar atomic rearrangements, the relative activation barrier ($\Delta\Delta^{\neq}G_L^S$) accompanying them is 5.6 kcal mol^{-1}. It is observed that in **IVt** the lone-pair occupancy on N^1 (1.822 e) is reduced due to hyperconjugation from the neighbouring H^2 and H^4 atoms (Figure 5). A similar situation is also present in **IVc**, although to a lesser extent, where the hyperconjugation is only effective with H^2, leading to a higher lone-pair occupancy on nitrogen (1.861 e). Therefore, the transition state involving proton transfer towards N^1 is facilitated for **IVc** rather than **IVt**. The shorter N^1–C^2 bond length in **IVt** than **IVc** [$r_{N^1-C^2}$(**IVc**/**IVt**) = 1.56/1.43 Å] supports indirectly the magnitude of this hyperconjugative effect. From **IVc**, there remains another possibility for intramolecular proton exchange between $O^1H^5\cdot\cdot O^3/C^4H^6\cdot\cdot O^1$ partners. The distorted six-membered transition state **IVc**–**11 l** (solid line in Figure 3) depicting this exchange entails a lowest activation barrier of 25.6 kcal mol^{-1}. Unfortunately, a similar route is unlikely for **IVt** as the incoming sesamol is oriented *anti* to the $CH_2O^1H^5$ group (see the Supporting Information, Figure S3).

From the calculated energies represented in Scheme 5 and Figures 3–5, the re-aromatization step is essentially rate determining. On the basis of kinetic investigations, Forlani et al. reported a similar finding whereby the step involving re-aromatization is rate limiting in the aromatic electrophilic substitution reaction.[19] The lowest energy route for formation of **11 l** is via the intramolecular proton exchange involving the distorted six-membered transition state **IVc**–**11 l**. On the other hand, the lowest energy path for **IVt** → **3 l** transformation is via transition state **IVt-ts2** (see the Supporting Information, Figure S3, -----). Clearly the formation of **11 l** is more favorable than **3 l** by 8.1 kcal mol^{-1}, which is in accordance with experimental observation. Therefore, we can justify that $CH_2O^1H^5$ plays a significant role in furnishing the *cis* product (**11 l**) via intramolecular proton exchange.

We also explored possibilities with other substituents, such as a methyl group instead of the CH_2OH unit in **9**. Herein, we have not considered step I of the reaction for the Me-substituted analogue of **9**, since the CH_2OH group doesn't play an additional role in this step. Therefore, we will directly discuss step II, originating from ylide intermediate **III-Me**. Similar reaction steps to those for **III** are followed by **III-Me** (for energy profiles, see the Supporting Information, Figures S4 and S5). Analogous *cis*- and *trans*-isomeric products resulting from the coupling of sesamol with **III-Me** are **13 h** and **3 h** respectively.[16] Not surprisingly, the re- aromatization step is rate limiting. The highest activation barrier for **13 h** formation is 5.0 kcal mol^{-1} lower than the corresponding step involved in **3 h** formation [$\Delta^{\neq}G_L^S$(**IVc-ts2-Me**/**IVt-ts1-Me**) = 30.3/35.3 kcal mol^{-1},

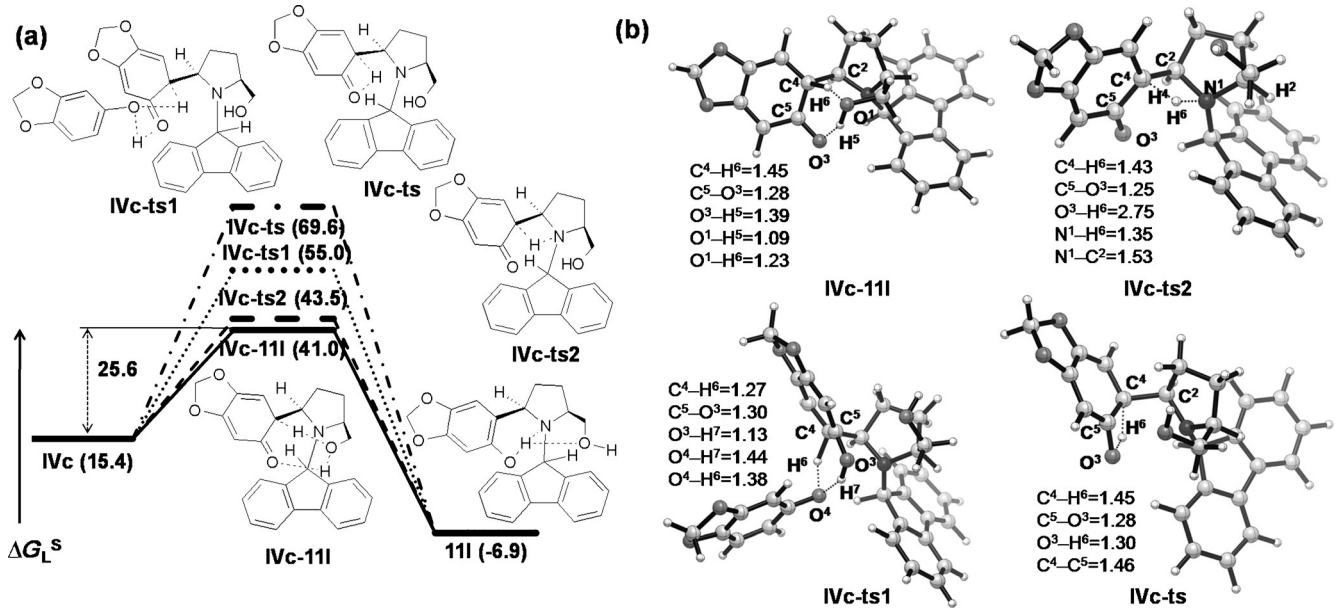


Figure 5. a) Energy profile for re-aromatization of **IVc**. Each line represents a different route of re-aromatization step (see text); b) optimized geometries of transition states. For energy and other conventions, refer to Figure 3.

solid/dashed line in Figure S4/S5, ——/-----]. Notably, substitution of CH_2OH by Me follows a similar mechanistic scenario, providing a clear advantage for formation of the *cis*- isomeric product. The relative activation barrier for the stereoisomeric product formation in the presence ofthe Me substituent is lower than that with CH_2OH ($\Delta\Delta^{\neq}G^{S}_{L}$(Me/$CH_2OH$) = 5.0/8.1 kcal mol^{-1}), indicating the effect of the latter in stabilization of the **IVc–11l** transition state (see above).

Reaction in ethanol

In polar media like ethanol, the reaction prefers alternate routes at two particular steps: dehydration of **II** and nucleophilic attack at **III**. Dehydration of **II** results in ionic species, whose formation is accelerated in polar media. However these species are prone to deactivation through coordination of other nucleophiles present in the medium. During this step, both ethanol (the solvent in this case) as well as sesamol can act as proton donors to form the ionic species **II-OH** (see the Supporting Information, Figure S1). However, the sesamol-assisted pathway (see the Supporting Information, Figure S1, ——) is more favorable than the ethanol-assisted one (-----) by 17.3 kcal mol^{-1}, because the conjugate base of sesamol (RO^-) is more stabilized than EtO^- by electron delocalization. The nucleophilic attack of EtO^- at C^3 of **II-OH** evidently forms a stable intermediate **III-OEt**, which is 4 kcal mol^{-1} less stable than intermediate **II**. A similar type of deactivation occurs during nucleophilic addition to **III** (see the Supporting Information, Figure S6). We mentioned previously that nucleophilic addition of sesamol to **III** occurs in a single step to avoid the formation of ionic species **III-P** (see above) under toluene medium. However, in polar solvents such as ethanol, **III-P** is stabilized by 40.4 kcal mol^{-1} (Figure 4a and Figure S6 in the Supporting Information). In the subsequent step, EtO^-coordination to **III-P** would yield unwanted stereoisomeric species **IVc-OEt** and **IVt-OEt**, those which are less stable than the starting materials by 4.9 and 3.9 kcal mol^{-1}, respectively (Figure S6). Therefore, such deactivations of ionic intermediates are responsible for a substantial reduction in the yield of the desired product under ethanol solvent.

Conclusion

In summary, highly regio- and stereoselective and enantiospecific direct C–H arylation of substituted pyrrolidine was achieved under metal- and oxidant-free reaction conditions, producing a variety of *syn*-2,5-disubstituted pyrrolidines with excellent enantiomeric excesses. In the reaction, facial selectivity, regioselectivity, and racemization were controlled to provide one out of six possible isomers. Optically active arylated pyrrolidine was shown to be useful for the easy and efficient synthesis of structural analogues of RP 66803 and ACE inhibitors. Furthermore, DFT calculations were performed to explore the mechanistic route for the selective C–H arylation reaction, correlating strongly with the experimental results.

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Keywords: amines · arylation · C–H activation · density functional calculations · stereoselectivity

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[15] CCDC 1062485 (**11 f**), 1062553 (**11 g**), 1059663 (**11 l**) and 1059394 (**13 a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] Compounds **11 l**, **3 l**, and **4 l** are equivalent to **2**, **3**, and **4** respectively, with Ar = sesamol and R = CH_2OH. Compounds **13 h** and **3 h** corresponds to **2** and **3** with Ar = sesamol and R = CH_3.

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