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Domino Imino-Aldol−Aza-Michael Reaction: One-Pot Diastereo- and Enantioselective Synthesis of Piperidines

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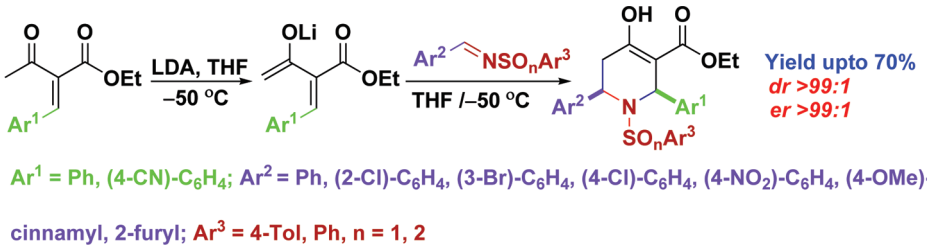

Addition of α-arylmethylidene- or α-alkylidene-β-keto ester enolate to *N*-activated aldimines via the imino aldol pathway followed by intramolecular aza-Michael reaction in a domino fashion has been developed, and a highly diastereoselective route to substituted piperidines is reported. Enantiopure piperidines are synthesized from chiral sulfinyl imines. Formation and the observed stereoselectivity of the products have been rationalized by mechanistic and computational studies.

Introduction

Piperidine rings are prevalent in the core structure of many naturally occurring alkaloids and drugs.[1] Substituted piperidines, particularly, 2- and/or 2,6-disubstituted piperidines are synthetically very important[2,3] and exhibit a wide spectrum of biological activities such as antibacterial, antifungal, and anti-HIV properties, etc.[2n] Immense synthetic and pharmacological utilities of such piperidines have inspired researchers to develop new strategies for their syntheses.

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Toward this end, several efforts have been devoted[4−13] mostly from substituted pyridines,[5a] amino alcohols,[5b−f] imines,[5g−k] aldol reaction,[5l] reductive amination reactions,[5m−p] ring expansion and heterocyclic rearrangements,[5q−u] aza-conjugate additions,[6] various metal- and acid-catalyzed cyclizations,[7] Mannich-type reactions,[8] olefin metathesis,[9] and hetero-Diels−Alder reactions,[10] etc. It is still challenging for organic chemists to develop more efficient synthetic routes toward functionalized piperidines with structural diversity and high diastereo- as well as enantioselectivity.

In this regard, Noller et al. and others have made significant contributions[11,12] via a multicomponent reaction protocol involving ketones or 1,3-dicarbonyl compounds, aldehydes, and amines. However, this approach has limitations in terms of the substrate scope and formation of racemic products. Previously, we reported the synthesis of racemic monosubstituted piperidines from the corresponding δ-amino-β-keto esters generated from the reaction of 1,3-dicarbonyl dianion of ethyl acetoacetate and imines.[13] In continuation of our research activity in enolate[14] and dianion[13] chemistry, we anticipated that a simple strategy involving a domino intermolecular imino-aldol followed by an intramolecular aza-Michael reaction would lead to the stereoselective formation of 2,6-disubstituted piperidines. In recent years, domino reactions[15] have become very fascinating and promising tools in synthetic organic chemistry over classical reactions considering reaction time, purification of the intermediates, and selectivity. We have successfully developed a simple one-pot, two-step strategy for the synthesis of highly funcionalized piperidines in diastereo- as well as enantiopure forms employing imino-aldol and aza-Michael reactions in a domino fashion (Scheme 1). Herein, we report our results in detail.

Results and Discussion

Our strategy involves (i) the synthesis of α-arylmethylidene- (**1a**,**b**) and α-alkylidene-β-keto ester (**1c**) as the precursor compounds and (ii) generation of the enolate from **1** followed by reaction with *N*-sulfonylaldimines. For this purpose, the precursors **1a**−**c** have been synthesized on the basis of literature procedures.[16] We have judiciously utilized these substrates as nucleophiles as well as electrophiles in the same reaction sequence, although **1a** has been used earlier as a good Michael acceptor.[17] To evaluate the feasibility of our approach, first the enolate was generated from compound (*E*)-**1a** by the treatment with LDA at −50 °C in THF and reaction with 2-phenyl-*N*-tosylaldimine **3a** to afford the corresponding 2,6-disubstituted piperidine **6a** in 65% yield as a single diastereomer (Scheme 1) with 2,6 *cis*-appendages as confirmed by X-ray crystallographic data.

Formation of *cis*-**6a** as the only diastereomer was confirmed by the ^{1}H NMR spectrum of the crude reaction mixture as it indicated the absence of other diastereomer. Presumably, the reaction followed a domino imino-aldol−aza-Michael reaction sequence. Interestingly, (*Z*)-**1a** produced the identical product (**6a**) under the same reaction conditions with lower yield. To generalize the methodology, a number of activated aldimines were reacted with compound

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SCHEME 1. Reaction of α-Arylmethylidene-β-keto Ester with 2-Aryl-*N*-sulfonylaldimines via Domino Imino-Aldol−Aza-Michael Sequence

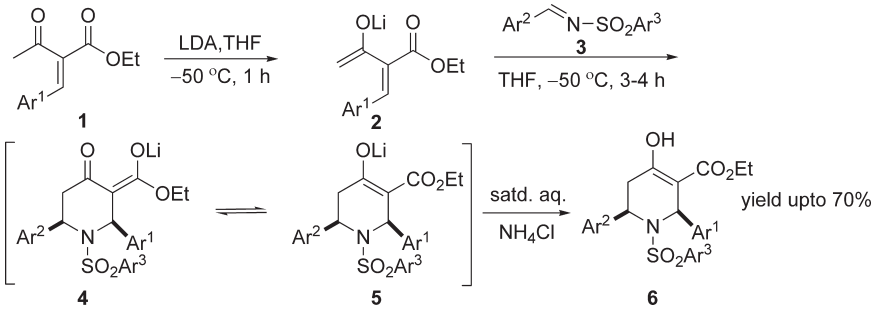

TABLE 1. Synthesis of 2,6-Disubstituted Piperidines

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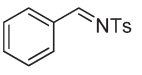
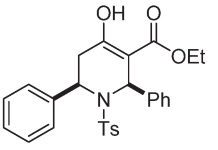
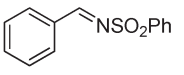
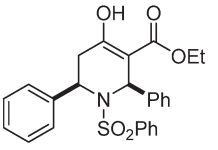
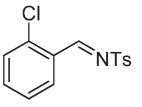
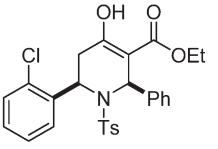
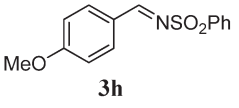
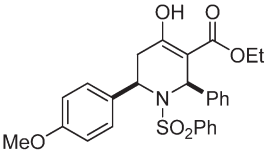
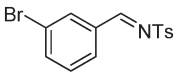
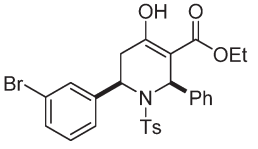
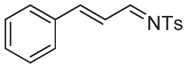
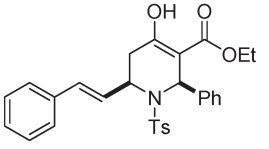
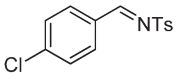
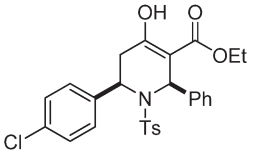
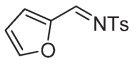
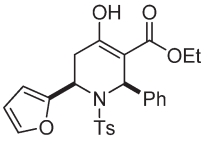
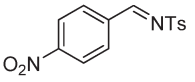
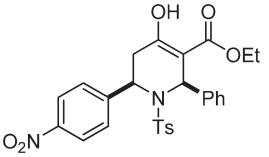
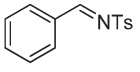
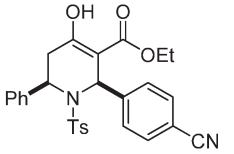
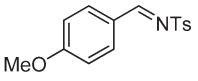
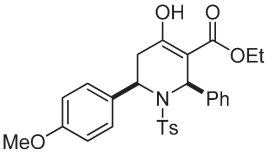
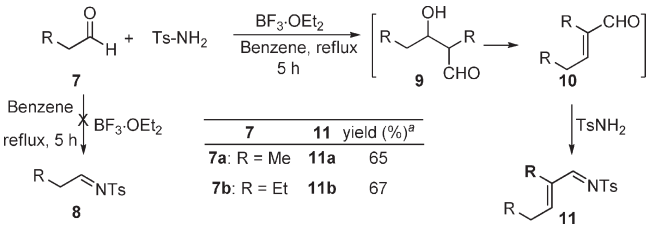
 **3a**	 **6a**, 65	 **3g**	 **6g**, 64
 **3b**	 **6b**, 66	 **3h**	 **6h**, 62
 **3c**	 **6c**, 63	 **3i**	 **6i**, 63
 **3d**	 **6d**, 68	 **3j**	 **6j**, 66
 **3e**	 **6e**, 70	 **3a**	 **6k**, 62
 **3f**	 **6f**, 58		

[a]Product was obtained as a single diastereomer in all the cases. [b]Ar^1 = Ph for **6a-6j** and Ar^1 = 4-CN-C_6H_4 for **6k**. [c]Yields of isolated products after column chromatographic purification.

SCHEME 2. Synthesis of 2-Alkenyl-*N*-tosylaldimines[a]



[a]Yields of isolated products after column chromatographic purification.

(*E*)-**1a**, and the results are shown in Table 1. The structures of other piperidines **6e** and **6j** as well as the *cis*-stereochemistry between the substituents at the 2 and 6 positions were confirmed by X-ray crystallographic data.[18] Furthermore, the piperidines **6** were found to exist in enol forms.

Next, the substrate scope of the strategy was explored by studying the reaction with aliphatic imines. To prepare such imines following an identical procedure used by us for aromatic imines, when aliphatic aldehyde **7** was treated with *p*-toluenesulfonamide in the presence of catalytic $BF_3 \cdot OEt_2$ in refluxing benzene, interestingly, the expected imine **8** was not formed; instead the imine **11** from the corresponding aldehyde **10** arising from the aldol condensation of aldehyde **7** was formed in good yield (Scheme 2). Formation of such a type of imine was precedented using a stoichiometric amount of trifluoroacetic anhydride, α-hydrogen-containing aliphatic aldehyde, and *p*-toluenesulfonamide.[19]

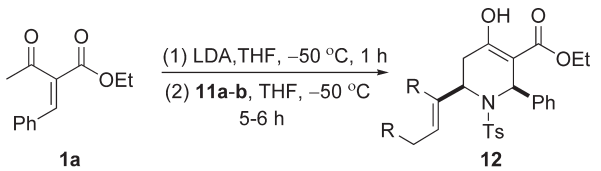
When the enolate of compound (*E*)-**1a** reacted with the imine **11a** following identical reaction conditions as shown in Scheme 1, the corresponding piperidine **12a** was obtained in 58% yield as a single diastereomer. Once again, the relative stereochemistry at the 2 and 6 positions was found to be *cis* from X-ray crystallographic data.[15] A similar result was obtained from (*E*)-**1a** and **11b** in the same reaction sequence (Scheme 3).

To demonstrate the synthetic potential of the strategy, next the reaction was explored with sulfinyl imine as a chiral source. Earlier sulfinyl imines were utilized by Davis et al.[2e−m,20] for the synthesis of nonracemic piperidines by an alternate strategy. Following our approach when the enolate generated from compound (*E*)-**1a** was treated with 2-phenyl-*N*-sulfinylaldimine **13a** the corresponding 2,6-disubstituted piperidine **14a** was obtained as a single diastereomer in enantiopure form (dr >99:1, er >99:1).

However, the reaction with sulfinyl imines takes a longer time and requires larger amounts of enolate (2.5 equiv) compared to sulfonyl imines. Further generalization to this approach was made with other sulfinylimines (Scheme 4, Table 2). Similar to previous cases, the *cis*-stereochemistry between the substituents at the 2- and 6-positions of piperidines **14a**−**d** was confirmed by the crystal structure of **14c**[18] as a representative example, and its absolute configuration was determined to be (2*R*,6*R*).

Furthermore, **14c** and **14d** were oxidized[21] to the corresponding tosyl derivatives (2*R*,6*R*)-**6d** and (2*R*,6*R*)-**6f**,

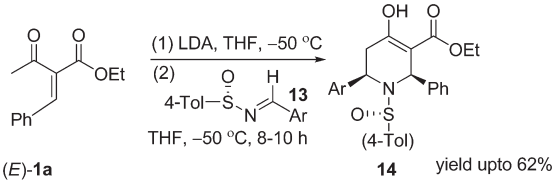
SCHEME 3. Reaction of α-Benzylidene-*β*-keto Ester with 2-Alkenyl-*N*-tosylaldimines[a]



	12[a]	Yield[b]
11a: R = Me	**12a**	58%
11b: R = Et	**12b**	56%

[a]Product was obtained as a single diastereomer in both cases. [b]Yields of isolated products after column chromatographic purification.

SCHEME 4. Reaction of α-Benzylidene-*β*-keto Ester with 2-Aryl-*N*-sulfinylaldimines



13a: Ar = Ph; **13b**: Ar = 4-NO_2-C_6H_4; **13c**: Ar = 4-Cl-C_6H_4; **13d**: Ar = 4-OMe-C_6H_4

respectively, in enantiopure forms (Scheme 5), and the er was determined by chiral HPLC analysis (see the Supporting Information). From these results, it is apparent that the compounds **14a**−**d** were produced in enantiomerically pure forms.

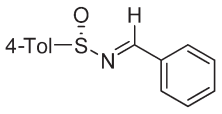
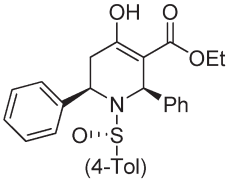
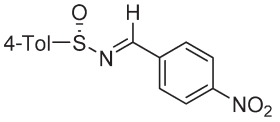
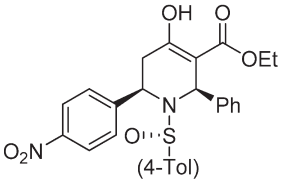
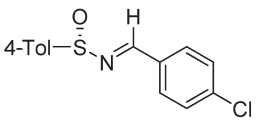
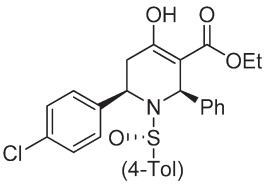
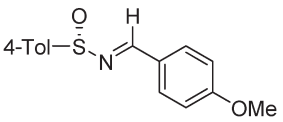
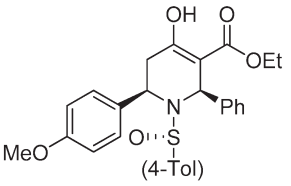
Crystal structures reveal that the piperidine molecules **6a**, **6e**, **6j**, **12a**, and **14c** exist in half-chair conformations where the 2,6-substituents occupy pseudoaxial and axial positions, respectively, and remain almost parallel to each other probably because of a favorable $\pi-\pi$ stacking interaction between them.

On the basis of the experimental results, NMR studies,[22] and X-ray crystallographic data,[18] the proposed mechanism for the formation of *N*-tosyl-2,6-diphenylpiperidine **6a** is shown in Scheme 6. The enolate **2** reacts with 2-phenyl-*N*-tosylaldimine **3a** to form the adduct **15**, which undergoes intramolecular aza-Michael reaction through the more favorable transition state **16a** to furnish **6a** via the intermediate **17a**. However, because of allylic strain between the phenyl and the CO_2Et groups, **17a** becomes less stable and flips to the thermodynamically more stable diaxial isomer **6a**, which is stabilized by a strong $\pi-\pi$ stacking interaction[23] between the Ph groups. Since **16a′** is the less favorable transition state probably because of a 1,3-diaxial interaction between the phenyl and hydrogen groups, the *trans*-isomer **6a′** does not form at all.

The methodology was further extended to the alkylidene substrate **1c**. When α-cyclohexylmethylidene-*β*-keto ester (*E*)-**1c** was reacted with 2-phenyl-*N*-tosylaldimine **3a**, interestingly the corresponding piperidine **18a** was formed with

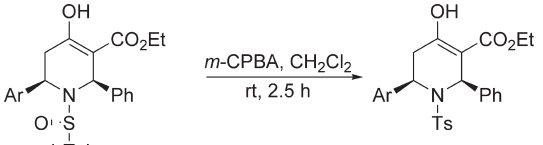
(18) For details of X-ray crystallographic analysis of **6a**,**e**,**j**, **12a**, **14c**, and **18a**,**b**, see the Supporting Information.
(19) Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett*. **2003**, *44*, 1231.
(20) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem*. **1995**, *60*, 7037.
(21) Davis, F. A.; Srirajan, V. *J. Org. Chem*. **2000**, *65*, 3248.
(22) The equatorial protons at the 2,6-positions of piperidine are far apart; they did not show any NOE interaction although they are *cis* to each other.
(23) For a recent study on $\pi-\pi$ stacking interaction supported by molecular modeling, see: Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M.; Speybroeck, V. V. *J. Org. Chem*. **2010**, *75*, 885.

TABLE 2. Synthesis of Chiral Piperidines from 2-Aryl-*N*-sulfinylaldimines

entry	Sulfinyl imine (**13**)	Chiral piperidine (**14**)[a]	Yield (%)[b]
1	 **13a**	 **14a**	55
2	 **13b**	 **14b**	58
3	 **13c**	 **14c**	62
4	 **13d**	 **14d**	53[c]

[a]Product was obtained as a single diastereomer in all cases. [b]Yields of isolated products after column chromatographic purification. [c]Yield of the product was determined after oxidation of sulfinyl group to tosyl group.

SCHEME 5. Oxidation of *N*-Sulfinyl 2,6-Disubstituted Piperidines to *N*-Tosyl 2,6-Disubstituted Piperidines



		yield	er
14c: Ar = 4-Cl-C_6H_4	(2*R*, 6*R*)-**6d**	65%	>99:1
14d: Ar = 4-OMe-C_6H_4	(2*R*, 6*R*)-**6f**	65%	>99:1

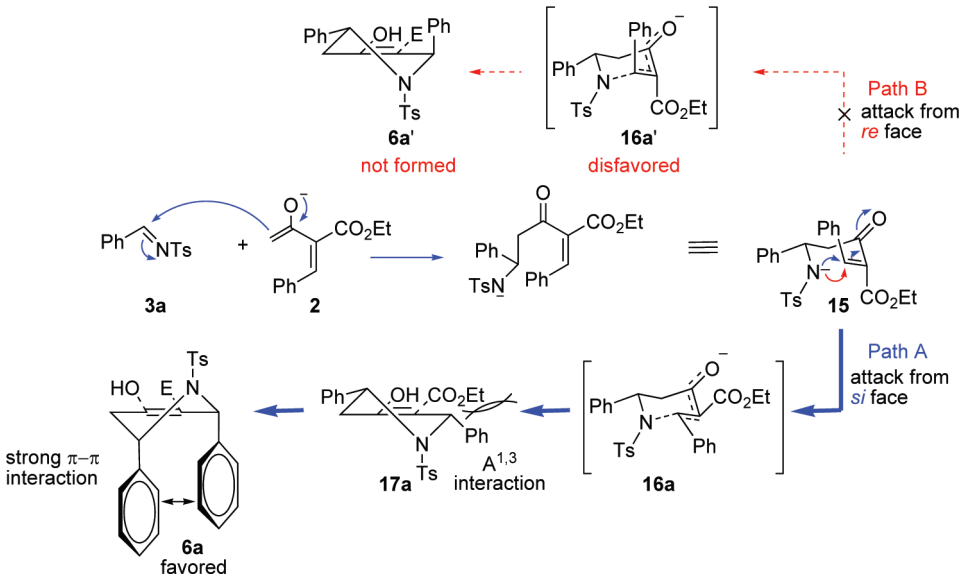
2,6 *cis*-appendages whereas (*Z*)-**1c** produced the corresponding piperidine **18b** with *trans*-stereochemistry as observed in its crystal structure (Scheme 7).[18]

It is worth noting that the piperidine **6a** has been formed as the sole product in the case of **1a** (*E* and *Z*), whereas for **1c** (*E* and *Z*), different diastereomeric products (**18a** and **18b**) have been observed depending on the double-bond geometry of the substrate.

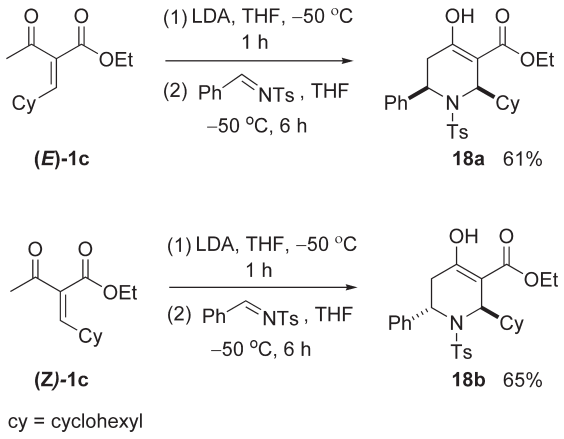
The mechanism for the formation of **18a**,**b** from **1c** is shown in Scheme 8. Compound **1c** (*E* and *Z*) follows a similar mechanism as described above for (*E*)-**1a**. The enolate from (*E*)-**1c** reacts with **3a** to form the adduct **19a**, which undergoes intramolecular aza-Michael reaction through the more favorable transition state **20a** to produce the *cis*-piperidine **18a** via the intermediate **21a**. Probably because of the allylic strain between the equatorial cyclohexyl and CO_2Et groups, **21a** is less stable and it flips to the thermodynamically most stable diaxial isomer **18a**, which is stabilized by a C−H-π stacking interaction between the axial hydrogen of the cyclohexyl ring and the axial phenyl group. The other possible TS **20a′** is less stabilized than **20a** probably because of 1,3-diaxial interaction between axial hydrogen and cyclohexyl groups; moreover, there is no $\pi-\pi$ stacking interaction between the Ph and Ts groups as discussed below for TS **20b**. Hence, the *trans*-piperidine **18b** did not form.

In the case of (*Z*)-**1c** the *trans*-piperidine **18b** was formed solely as the kinetically controlled product through the more favorable transition state **20b** at lower temperature (−50 °C). Probably because of a weak $\pi-\pi$ stacking interaction between the Ph and Ts groups, **20b** is more stabilized than the other possible TS **20b′**. Hence, the *cis*-piperidine **18a** did not form at lower temperature.

SCHEME 6. Proposed Mechanism and Favorable Transition State for the Formation of 6a



SCHEME 7. Reaction of (*E*)- and (*Z*)-α-Cyclohexylmethylidene-*β*-keto Ester with 2-Phenyl-*N*-tosylaldimine



These observations are further supported by the computational studies.[24] In the cases of both diaryl- and cyclohexyl-aryl-substituted piperidines, the *cis*-isomer is found to be thermodynamically more stable and remains in a diaxial conformation. But the energy difference between the *cis*- and *trans*-isomers of diaryl piperidines (1.71 kcal/mol for **6a**) is found to be larger compared to the cyclohexyl−aryl analogue (0.66 kcal/mol for **18**). For this reason, in the case of diarylpiperidines, the *cis*-product **18a** was always observed. In the case of substrate (*Z*)-**1c**, the *trans*-product **18b** was observed as the only product at lower temperature (−50 °C). Since the energy difference between the *cis*- and *trans*-isomers of cyclohexylphenylpiperidines (**18a** and **18b**) is very small, it is expected that at higher temperature the thermodynamically more stable *cis*-isomer will be formed along with the *trans*-isomer. This is, in fact, supported by experimental results. In a separate experiment when the temperature of the reaction mixture from (*Z*)-**1c** was raised to room temperature (25 °C), the thermodynamically more stable isomer **18a** started forming. After the same mixture was reacted at room temperature for 7 h both **18a** and **18b** were formed in ∼1:1 ratio (Scheme 8).[25]

Conclusion

In conclusion, we have developed a simple diastereo- as well as enantioselective synthetic route to highly functionalized piperidines via a domino imino-aldol−aza-Michael reaction sequence. This strategy has been generalized for aromatic, heteroaromatic, aliphatic, as well as chiral sulfinyl imines. It is possible to obtain 2,6 *cis*- or *trans*-disubstituted piperidines depending on the substrates (α-arylmethylidene- or α-alkylidene-*β*-keto ester) and their *E*/*Z* geometry. Formation and the observed stereoselectivity of the products have been explained by plausible mechanisms and further supported by computational studies. Further synthetic and mechanistic studies are in progress.

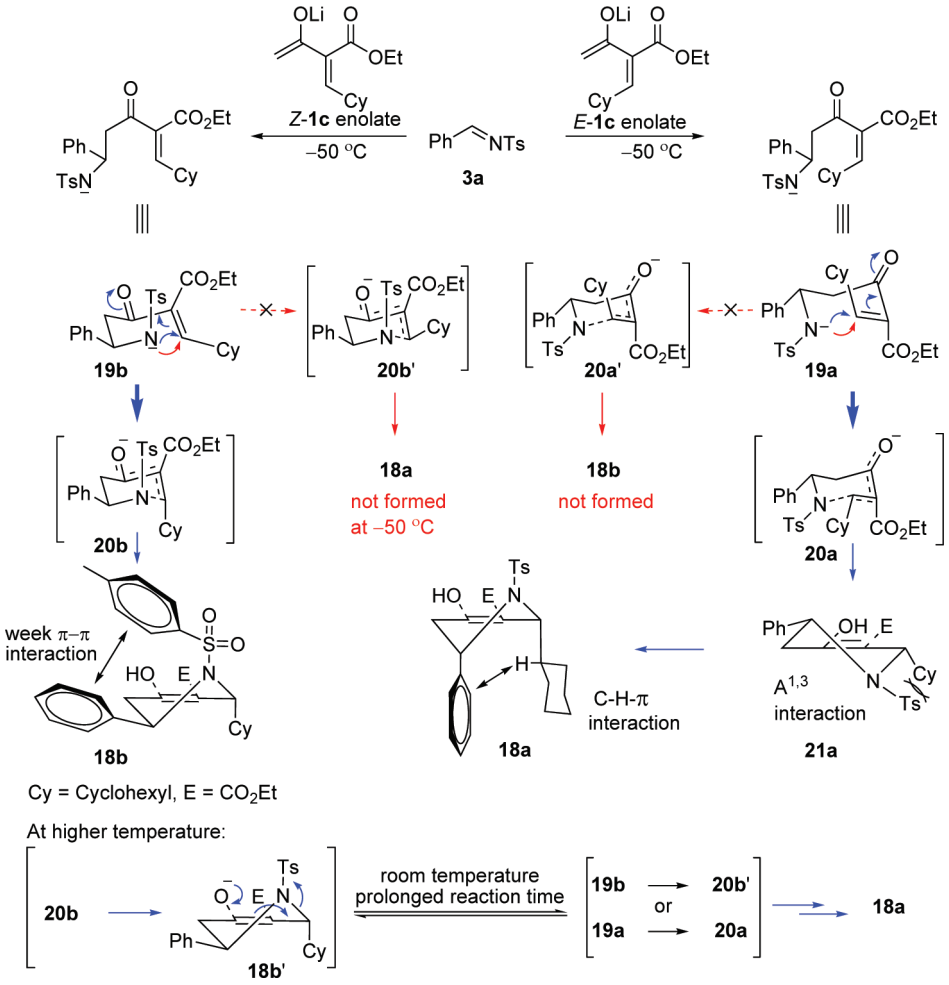
Experimental Section

Procedure for the Synthesis of Ethyl 2-Benzylidene-3-oxobutanoate (1a).[16b] To a solution of L-proline (0.33 g, 2.83 mmol) in 15.0 mL of dry DMSO was added 0.95 mL of benzaldehyde (1.0 g, 9.42 mmol), the mixture was stirred for 8−10 min at room temperature, and then ethyl acetoacetate (1.44 mL, 11.31 mmol) was added slowly into it at the same temperature and stirred for 12−14 h. After completion of the reaction as monitored by TLC, 20.0 mL of ethyl acetate was added, the mixture was stirred for a few minutes, and then the reaction was quenched with cold water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15.0 mL), washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude

(24) Computational study of the compounds **6a**, *trans*-**6a**, and **18a**,**b** has been performed with the Gaussian 03 program using the B3LYP exchange corelation functional with a 6-31G* basis set. For more details, see the Supporting Information.

(25) Following an identical procedure as described for **6a** in the Experimental Section, after the addition of the imine at −50 °C, the reaction was warmed to room temperature and stirred at the same temperature for additional 7 h. After usual workup, the ^{1}H NMR of the crude reaction mixture indicated the formation of **18a** and **18b** in ∼1:1 ratio. See the Supporting Information for the ^{1}H NMR spectrum of the crude reaction mixture containing **18a** and **18b**.

SCHEME 8. Proposed Mechanism and Favorable Transition States for the Formation of 18a and 18b



reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 5% ethyl acetate in petroleum ether to afford **1a** (1.54 g) in 75% yield as a mixture of two diastereomers (*E*)-**1a** (0.42 g) and (*Z*)-**1a** (1.12 g) in a ratio of 1:2.7 (determined by ^{1}H NMR spectra of the crude product).

(*E*)-Ethyl 2-Benzylidene-3-oxobutanoate ((*E*)-1a). The general procedure described above was followed to afford (*E*)-**1a** as a light yellow solid: mp 45−46 °C; R_f 0.46 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3385, 3059, 3028, 2981, 2926, 2121, 1959, 1884, 1697, 1620, 1449, 1379, 1353, 1319, 1294, 1256, 1212, 1183, 1086, 1061, 1024, 969, 943, 862, 773, 755, 711, 693, 619, 528, 476, 446; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.1 Hz), 2.35 (s, 3H), 4.3 (q, 2H, J = 7.1 Hz), 7.39 (s, 5H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 31.2, 61.5, 128.9, 129.6, 130.4, 132.9, 134.1, 140.5, 164.4, 203.3; HRMS (ESI) calcd for $C_{13}H_{15}O_3$ ($M + H^+$) 219.1021, found 219.1021.

(*Z*)-Ethyl 2-Benzylidene-3-oxobutanoate ((*Z*)-1a). The general procedure described above was followed to afford (*Z*)-**1a** as a light yellow solid: mp 46−48 °C; R_f 0.34 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3432, 3089, 3051, 2985, 2935, 2873, 1974, 1905, 1724, 1658, 1616, 1572, 1494, 1450, 1399, 1347, 1330, 1315, 1291, 1243, 1222,1205, 1189, 1153, 1116, 1085, 1039, 1014, 948, 933, 899, 874, 861, 837, 812, 761, 693, 611, 588, 545, 465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 2.43 (s, 3H), 4.34 (q, 2H, J = 7.1 Hz), 7.39 − 7.47 (m, 5H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 26.4, 61.6, 128.8, 129.4, 130.6, 132.8, 134.5, 141.2, 167.7, 194.6; HRMS (ESI) calcd for $C_{13}H_{15}O_3$ ($M + H^+$) 219.1021, found 219.1029.

Procedure for the Synthesis of Ethyl 2-(4-Cyanobenzylidene)-3-oxobutanoate (1b)[16c]. To a suspension of $Mg(ClO_4)_2$ (0.64 mmol) and $MgSO_4$ (1.27 mmol) in 10.0 mL of THF were added 4-cyanobenzaldehyde (1.0 g, 7.63 mmol) and ethyl acetoacetate (0.81 mL, 6.35 mmol) at room temperature, and the mixture was stirred at the same temperature for 70 h. After completion of the reaction, as monitored by TLC, 15.0 mL of CH_2Cl_2 was added, and the reaction mixture was filtered through Celite. The solvent was evaporated under reduced pressure to afford the crude reaction mixture as a mixture of two diastereomers which was purified by flash column chromatography on silica gel (230−400 mesh) using 8% ethyl acetate in petroleum ether to afford **1b** (1.42 g) in 76% yield as a mixture of two diastereomers (*E*)-**1b** (0.41 g) and (*Z*)-**1b** (1.01 g) in a ratio of 1:2.5 (determined by ^{1}H NMR spectra of the crude product).

(*E*)-Ethyl 2-(4-Cyanobenzylidene)-3-oxobutanoate ((*E*)-1b). The general procedure described above was followed to afford (*E*)-**1b** as a white solid: mp 64−65 °C; R_f 0.44 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3442, 2984, 2229, 1730, 1669, 1504, 1383, 1297, 1244, 1042, 828, 559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 2.29 (s, 3H), 4.20−4.30 (m, 2H), 7.19 (s, 1H), 7.52−7.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 31.2, 61.9, 113.6, 118.0, 129.9, 132.5, 136.9, 138.0, 138.5, 163.8, 202.1; HRMS (ESI) calcd for $C_{14}H_{14}NO_3$ ($M + H^+$) 244.0973, found 244.0972.

(*Z*)-Ethyl 2-(4-Cyanobenzylidene)-3-oxobutanoate ((*Z*)-1b). The general procedure described above was followed to afford (*Z*)-**1b** as a white solid: mp 66−68 °C; R_f 0.37 (30% ethyl acetate

in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3443, 2983, 2226, 1732, 1661, 1627, 1385, 1298, 1249, 1224, 1206, 1043, 923, 828, 560; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.1 Hz), 2.37 (s, 3H), 4.22−4.28 (m, 2H), 7.41−7.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 26.8, 62.0, 113.7, 118.0, 129.6, 132.4, 137.6, 138.5, 166.8, 193.8; HRMS (ESI) calcd for $C_{14}H_{14}NO_3$ ($M + H^+$) 244.0973, found 244.0975.

Procedure for the Synthesis of Ethyl 2-(Cyclohexylmethylene)-3-oxobutanoate (1c)[16b]. To a solution of L-proline (0.31 g, 2.7 mmol) in 15.0 mL of dry DMSO was added 1.08 mL of cyclohexyl carboxaldehyde (1.0 g, 8.92 mmol), the resulting solution was stirred for 8−10 min at room temperature, and then ethyl acetoacetate (1.36 mL, 10.7 mmol) was added slowly at the same temperature followed by stirred for 12−14 h. After completion of the reaction as monitored by TLC, 20.0 mL ethyl acetate was added, the mixture was stirred for a few minutes, and then the reaction was quenched with cold water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15.0 mL), washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 5% ethyl acetate in petroleum ether to afford **1c** (1.56 g) in 78% yield as a mixture of two diastereomers (*E*)-**1c** (0.58 g) and (*Z*)-**1c** (0.98 g) in a ratio of 1:1.7 (determined by ^1H NMR spectra of the crude product).

(*E*)-Ethyl 2-(Cyclohexylmethylene)-3-oxobutanoate ((*E*)-1c). The general procedure described above was followed to afford (*E*)-**1c** as a colorless liquid: R_f 0.56 (15% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}) 3386, 2981, 2929, 2854, 1706, 1634, 1449, 1373, 1303, 1273, 1253, 1226, 1148, 1101, 1054, 966, 863, 762, 619, 565; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09−1.24 (m, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.64−1.73 (m, 6H), 2.29−2.33 (m, 1H), 2.35 (s, 3H), 4.17−4.30 (m, 2H), 6.69 (d, 1H, J = 10.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.2, 25.6, 26.9, 31.8, 39.3, 61.1, 135.3, 152.5, 166.7, 201.3; HRMS (ESI) calcd for $C_{13}H_{21}O_3$ ($M + H^+$) 225.1490, found 225.1499.

(*Z*)-Ethyl 2-(Cyclohexylmethylene)-3-oxobutanoate ((*Z*)-1c). The general procedure described above was followed to afford (*Z*)-**1c** as a colorless liquid: R_f 0.48 (15% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}) 3331, 2981, 2930, 2853, 1732, 1697, 1672, 1634, 1449, 1380, 1305, 1273, 1260, 1210, 1150, 1104, 1035, 967, 947, 909, 854, 792, 620, 564, 543; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06−1.24 (m, 6H), 1.27 (t, 3H, J = 7.3 Hz), 1.60−1.69 (m, 4H), 2.24 (s, 1H), 2.28−2.34 (m, 1H), 4.24 (q, 2H, J = 7.3 Hz), 6.56 (d, 1H, J = 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.1, 25.6, 26.8, 31.7, 39.2, 60.1, 135.2, 152.6, 166.6, 195.4; HRMS (ESI) calcd for $C_{13}H_{21}O_3$ ($M + H^+$) 225.1490, found 225.1496.

Procedure for the Synthesis of *N*-Tosyl 2,6-Disubstituted Piperidines. To a solution of diisopropylamine (0.08 mL, 0.55 mmol) in 2.0 mL of dry THF was added 2.0 M *n*-BuLi (0.28 mL, 0.55 mmol) at 0 °C and the mixture stirred for 30 min under argon atmosphere. The color of the solution changed to yellow, the temperature was dropped to −50 °C, compound (*E*)-**1a** (100 mg, 0.46 mmol) dissolved in 1.0 mL of dry THF was added slowly, and the resulting mixture was stirred for 1 h to allow the formation of enolate. Then 2-aryl-*N*-sulfonylaldimine **3a**−**j** (0.46 mmol) dissolved in 1.5 mL of dry THF was added and the mixture stirred for an additional 2−4 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 4% ethyl acetate in petroleum ether to afford the pure piperidines **6a**−**k** as a white solid. All these compounds exist in enol form as indicated by ^1H NMR spectra and crystal structure.

Compound (*E*)-**1a** and compound (*Z*)-**1a** were two diastereomers when separately reacted with 2-phenyl-*N*-tosylaldimine **3a**. Following same procedure described above, compound **6a** was obtained as the only product, and the relative stereochemistry in both cases was confirmed by ^1H NMR spectra and X-ray crystallographic analysis. The yield of product **6a** was different in both the cases (starting from of (*E*)-**1a**, the yield was 65% but from (*Z*)-**1a** it was only 40%).

4-Hydroxy-2,6-diphenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6a). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) was reacted with 119.0 mg (0.46 mmol) of **3a** (0.46 mmol) at −50 °C for 3.0 h to afford **6a** (142.8 mg, 65% yield) as a white solid: mp 162−164 °C; R_f 0.5 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3423, 3058, 2925, 1650, 1621, 1494, 1451, 1427, 1406, 1379, 1360, 1343, 1295, 1261, 1223, 1186, 1162, 1096, 1076, 1027, 992, 954, 917, 848, 814, 779, 753, 726, 696, 683, 656, 626, 578, 560, 531; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.3 Hz), 2.34 (dd, 1H, J = 6.9, 17.6 Hz), 2.45 (s, 3H), 2.62 (dd, 1H, J = 5.4, 17.6 Hz), 4.02−4.14 (m, 2H), 5.06−5.10 (m, 1H), 6.13 (s, 1H), 6.96−7.02 (m, 5H), 7.03−7.06 (m, 3H), 7.10−7.14 (m, 2H), 7.30 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.4 Hz), 12.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.6, 31.2, 54.1, 55.3, 60.8, 98.1, 126.7, 127.2, 127.3, 127.6, 127.7, 127.9, 129.8, 136.6, 139.3, 139.7, 143.8, 170.0, 170.7; HRMS (ESI) calcd for $C_{27}H_{28}NO_5S$ ($M + H^+$) 478.1688, found 478.1686.

6-(2-Chlorophenyl)-4-hydroxy-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6b). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) was reacted with 135.0 mg of **3b** (0.46 mmol) at −50 °C for 3.5 h to afford **6b** (155.4 mg, 66% yield) as a white solid: mp 175−178 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3425, 3065, 2924, 2855, 1662, 1632, 1597, 1493, 1451, 1411, 1356, 1290, 1262, 1230, 1164, 1090, 1042, 954, 817, 756, 734, 701, 661, 622, 564, 544, 470; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 2.28 (dd, 1H, J = 11.2, 16.4 Hz), 2.44 (s, 3H), 2.59 (dd, 1H, J = 5.8, 16.4 Hz), 4.10−4.30 (m, 2H), 5.13−5.21 (m, 1H), 6.25 (s, 1H), 6.90−7.11 (m, 3H), 7.15−7.32 (m, 4H), 7.33−7.41 (m, 2H), 7.53 (d, 2H, J = 7.3 Hz), 7.79 (d, 2H, J = 8.3 Hz), 11.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.6, 34.4, 55.4, 56.7, 60.9, 98.7, 127.2, 127.6, 127.9, 128.4, 128.5, 128.7, 129.2, 129.6, 131.5, 134.6, 139.5, 139.9, 144.0, 169.3, 172.2; HRMS (ESI) calcd for $C_{27}H_{27}ClNO_5S$ ($M + H^+$) 512.1298, found 512.1296.

6-(3-Bromophenyl)-4-hydroxy-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6c). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) was reacted with 155.0 mg of **3c** (0.46 mmol) at −50 °C for 3.5 h to afford **6c** (161.0 mg, 63% yield) as a white solid: mp 128−130 °C; R_f 0.47 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3424, 3056, 2924, 2854, 1667, 1624, 1432, 1403, 1372, 1346, 1301, 1224, 1158, 1094, 1075, 1026, 993, 958, 902, 813, 774, 741, 704, 660, 625, 561, 462; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7.3 Hz), 2.33 (dd, 1H, J = 7.3, 17.9 Hz), 2.44 (s, 3H), 2.55 (dd, 1H, J = 5.4, 17.9 Hz), 4.03−4.15 (m, 2H), 5.04−5.07 (m, 1H), 6.11 (s, 1H), 6.83−6.89 (m, 1H), 6.94 (d, 1H, J = 7.7 Hz), 7.02−7.14 (m, 7H), 7.30 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz), 12.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 30.7, 54.0, 54.7, 60.9, 98.1, 122.2, 125.8, 127.1, 127.2, 127.5, 127.8, 129.5, 129.9, 130.4, 130.6, 136.5, 139.3, 141.5, 144.0, 169.9, 170.2; HRMS (ESI) calcd for $C_{27}H_{27}BrNO_5S$ ($M + H^+$) 556.0793, found 556.0794.

6-(4-Chlorophenyl)-4-hydroxy-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6d). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 135.0 mg of **3d** (0.46 mmol) at −50 °C for 3.0 h to afford **6d** (160.0 mg, 68% yield) as a white solid: mp 145−148 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3444, 3063, 2924, 1656, 1621, 1494, 1433, 1405, 1343, 1298, 1222, 1162, 1095, 1029, 993, 957, 884, 825, 751, 715, 686, 657, 578, 541; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.1 Hz), 2.32 (dd, 1H, J = 7.1, 17.6 Hz), 2.45 (s, 3H), 2.57 (dd, 1H, J = 5.1, 17.8 Hz), 4.02−4.14 (m, 2H), 5.06−5.09 (m, 1H), 6.11 (s, 1H), 6.86−6.97 (m, 4H), 7.04−7.13 (m, 5H), 7.31 (d, 2H, J = 8.1 Hz), 7.76 (d, 2H, J = 8.3 Hz), 12.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.6, 30.8, 54.0, 54.5, 60.9, 98.1, 126.8, 127.2, 127.5, 127.8, 128.0, 128.7, 129.9, 136.5, 137.8, 139.5, 144.0, 169.9, 170.3; HRMS (ESI) calcd for $C_{27}H_{27}ClNO_5S$ ($M + H^+$) 512.1298, found 512.1296.

4-Hydroxy-6-(4-nitrophenyl)-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6e). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 140.0 mg of **3e** (0.46 mmol) at −50 °C for 3.0 h to afford **6e** (168.2 mg, 70% yield) as a white solid: mp 175−179 °C; R_f 0.33 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3447, 2981, 1659, 1628, 1600, 1517, 1494, 1435, 1404, 1345, 1307, 1267, 1227, 1186, 1162, 1092, 1024, 1007, 987, 923, 890, 851, 802, 741, 700, 679, 654, 619,564, 547, 464; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.1 Hz), 2.38 (dd, 1H, J = 7.1, 17.8 Hz), 2.46 (s, 3H), 2.61 (dd, 1H, J = 5.4, 17.8 Hz), 4.02−4.19 (m, 2H), 5.14−5.18 (m, 1H), 6.14 (s, 1H), 7.03−7.08 (m, 3H), 7.09−7.20 (m, 4H), 7.33 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.84 (d, 2H, J = 8.8 Hz), 12.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 30.7, 54.2, 54.8, 61.0, 98.2, 123.1, 127.2, 127.6, 127.9, 128.2, 130.0, 136.1, 139.2, 144.3, 146.8, 169.7; HRMS (ESI) calcd for $C_{27}H_{26}N_2O_7SNa$ ($M + Na^+$) 545.1358, found 545.1357.

4-Hydroxy-6-(4-methoxyphenyl)-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6f). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 133.0 mg of **3f** (0.46 mmol) at −50 °C for 4.0 h to afford **6f** (135.4 mg, 58% yield) as a white solid: mp 148−152 °C; R_f 0.4 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3448, 2924, 2854, 1741, 1657, 1513, 1458, 1426, 1403, 1376, 1343, 1300, 1256, 1232, 1160, 1097, 1031, 883, 813, 752, 731, 702, 686, 655, 623, 557, 465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.1 Hz), 2.25 (dd, 1H, J = 6.6, 17.3 Hz), 2.38 (s, 3H), 2.53 (dd, 1H, J = 4.9, 17.6 Hz), 3.61 (s, 3H), 3.92−4.09 (m, 2H), 4.99−5.02 (m, 1H), 6.03 (s, 1H), 6.43(d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 6.93−7.04 (m, 4H), 7.19 −7.27 (m, 3H), 7.70 (d, 2H, J = 8.3 Hz), 12.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 30.9, 53.9, 54.5, 55.2, 60.7, 98.0, 113.3, 126.5, 127.2, 127.5, 127.6 128.5, 129.8, 131.1, 136.8, 139.9, 143.7, 158.6, 170.1, 170.7; HRMS (ESI) calcd for $C_{28}H_{29}NO_6SNa$ ($M + Na^+$) 530.1613, found 530.1618.

1-Benzenesulfonyl-4-hydroxy-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6g). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 113.0 mg of **3g** (0.46 mmol) at −50 °C for 2.5 h to afford **6g** (136.4 mg, 64% yield) as a white solid: mp 184−186 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3447, 3034, 2925, 2855, 1963, 1663, 1630, 1496, 1451, 1425, 1402, 1370, 1341, 1302, 1233, 1163, 1096, 1026, 987, 925, 882, 782, 747, 692, 629, 578, 552, 464; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99, (t, 3H, J = 7.1 Hz), 2.27 (dd, 1H, J = 7.1, 17.6 Hz), 2.56 (dd, 1H, J = 5.6, 17.8 Hz), 3.93−4.09 (m, 2H), 5.01−5.05 (m, 1H), 6.07 (s, 1H), 6.90−6.99 (m, 8H), 7.05−7.08 (m, 2H), 7.42−7.48 (m, 2H), 7.52−7.57 (m, 1H), 7.83 (d, 2H, J = 8.6 Hz), 12.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 31.2, 54.3, 55.5, 60.8, 98.1, 127.3, 127.6, 127.7, 127.8, 128.0, 129.2, 133.0, 139.3, 139.5, 169.9, 170.8; HRMS (ESI) calcd for $C_{26}H_{26}NO_5S$ ($M + H^+$) 464.1531, found 464.1533.

1-Benzenesulfonyl-4-hydroxy-6-(4-methoxyphenyl)-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6h). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 126.0 mg of **3h** (0.46 mmol) at −50 °C for 3.5 h to afford **6h** (140.8 mg, 62% yield) as a white solid: mp 144−146 °C; R_f 0.32; (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3448, 2929, 1654, 1618, 1513, 1448, 1404, 1348, 1301, 1253, 1226, 1162, 1096, 1077, 1029, 990, 880, 829, 802, 753, 738, 695, 628, 576, 551, 465.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.1 Hz), 2.24 (dd, 1H, J = 7.1, 17.8 Hz), 2.53 (dd, 1H, J = 5.1, 17.8 Hz), 3.62 (s, 3H), 3.92−4.09 (m, 2H), 5.00−5.04 (m, 1H), 6.05 (s, 1H), 6.44 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.3 Hz), 6.95−7.06 (m, 5H), 7.42−7.49 (m, 2H), 7.52−7.58 (m, 1H), 7.82 (d, 2H, J = 8.3 Hz), 12.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 31.1, 54.1, 54.7, 55.2, 60.8, 98.0, 113.3, 127.2, 127.5, 127.6, 128.5, 128.6, 129.2, 131.1, 132.9, 139.7, 158.7, 170.0, 170.8; HRMS (ESI) for calcd $C_{27}H_{28}NO_6S$ ($M + H^+$) 494.1637, found 494.1633.

4-Hydroxy-2-phenyl-6-styryl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6i). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 131.0 mg of **3i** (0.46 mmol) at −50 °C for 3.0 h to afford **6i** (145.9 mg, 63% yield) as a white solid: mp 122−124 °C; R_f 0.48 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3448, 3030, 2925, 1653, 1623, 1493, 1450, 1425, 1404, 1342, 1304, 1260, 1219, 1184, 1160, 1092, 1021, 975, 917, 818, 801, 731, 695, 673, 613, 576, 551, 473; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, 3H, J = 7.1 Hz), 2.34−2.39 (m, 2H), 2.43 (s, 3H), 4.03−4.20 (m, 2H), 4.78−4.82 (m, 1H), 5.53−5.61 (m, 1H), 6.12 (s, 1H), 6.20 (d, 1H, J = 16.1 Hz), 6.83−6.91 (m, 2H), 7.12−7.23 (m, 5H), 7.25−7.30 (m, 3H),7.37 (d, 2H, J = 7.3 Hz), 7.74 (d, 2H, J = 8.3 Hz), 12.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 30.2, 53.0, 53.3, 60.8, 97.9, 126.4, 127.0, 127.1, 127.6, 128.0, 128.1, 128.2, 129.7, 129.8, 130.6, 136.0, 137.1, 140.6, 143.8, 170.3; HRMS (ESI) calcd for $C_{29}H_{29}NO_5SNa$ ($M + Na^+$) 526.1664, found 526.1667.

6-Furan-2-yl-4-hydroxy-2-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (6j). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 115.0 mg of **3j** (0.46 mmol) at −50 °C for 3.0 h to afford **6j** (141.9 mg, 66% yield) as a white solid: mp 172−176 °C; R_f 0.46 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3449, 2979, 2924, 1656, 1495, 1452, 1409, 1379, 1350, 1302, 1227, 1185, 1163, 1093, 1028, 966, 913, 886, 810, 733, 701, 672, 621, 595, 570, 549; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.1 Hz), 2.37 (s, 3H), 2.43 (dd, 1H, J = 7.6, 18.1 Hz), 2.55 (dd, 1H, J = 2.7, 18.3 Hz), 3.91−4.08 (m, 2H), 5.21 (d, 1H, J = 5.8 Hz), 5.78 (d, 1H, J = 3.2 Hz), 5.84−5.87 (m, 1H), 6.0 (s, 1H), 6.77 (s, 1H), 6.92−7.01 (m, 4H), 7.19−7.24 (m, 3H), 7.70 (d, 2H, J = 8.3 Hz) 12.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.7, 28.9, 47.9, 53.1, 60.8, 97.5, 108.6, 110.2, 126.4, 127.3, 127.5, 127.6, 129.9, 137.2, 139.7, 142.2, 143.9, 150.7, 169.9, 170.4; HRMS (ESI) calcd for $C_{25}H_{25}NO_6SNa$ ($M + Na^+$) 490.1300, found 490.1306.

Ethyl 2-(4-Cyanophenyl)-4-hydroxy-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (6k). The general procedure described above was followed when the enolate of **1b** (100.0 mg, 0.41 mmol) reacted with 106.0 mg of **3a** (0.41 mmol) at −50 °C for 3.5 h to afford **6k** (128 mg, 62% yield) as a white solid: mp

163−165 °C; R_f 0.32 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 2924, 2853, 2228, 1737, 1658, 1602, 1498, 1453, 1409, 1351, 1303, 1259, 1230, 1161, 1093, 1020, 954, 812, 756, 692, 659, 606, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.1 Hz), 2.1 (dd, 1H, J = 7.3, 18.3 Hz), 2.40 (s, 3H), 2.62 (dd, 1H, J = 2.0, 18.6 Hz), 3.90−4.06 (m, 2H), 5.20−5.22 (m, 1H), 6.0 (s, 1H), 6.82−6.95 (m, 5H), 6.99 (d, 2H, J = 8.3 Hz), 7.12 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.72 (d, 2H, J = 8.0 Hz), 12.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.8, 28.5, 52.9, 53.2, 61.1, 96.4, 109.9, 119.1, 127.1, 127.7, 127.8, 128.1, 128.3, 128.8, 130.3, 131.1, 136.9, 137.2, 144.4, 145.8, 170.0, 170.9; HRMS (ESI) calcd for $C_{28}H_{27}N_2O_5S$ (M + H^+) 503.1640, found 503.1647.

Procedure for the Synthesis of 2-Alkenyl-*N*-tosylaldimines. *p*-Toluenesulfonamide (2.0 g, 11.68 mmol) and aliphatic aldehyde **7** (17.52 mmol) were taken in 15.0 mL of benzene, and then $BF_3\cdot OEt_2$ (0.15 mL, 1.2 mmol) was added at room temperature and heated to reflux at 85−90 °C with a Dean−Stark apparatus for 5−6 h. After completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure, and then the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether as eluent to obtain pure aldimines **11a**,**b** as a white solid.

4-Methyl-*N*-((*E*)-2-methylpent-2-enylidene)benzenesulfonamide (11a). The general procedure described above was followed when 1.3 mL of propionaldehyde **7a** (1.02 g, 17.52 mmol) was reacted with 2.0 g of *p*-toluene sulfonamide (11.68 mmol) to afford **11a** (1.9 g, 65% yield) as a white solid: mp 40−42 °C; R_f 0.38 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3437, 2968, 2930, 2875, 1922, 1631, 1569, 1493, 1450, 1402, 1317, 1262, 1229, 1156, 1088, 1042, 913, 883, 843, 810, 772, 675, 607, 550, 491, 466; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.6 Hz), 1.84 (s, 3H), 2.34−2.42 (m, 2H), 2.43 (s, 3H), 6.52 (t, 1H, J = 7.3 Hz), 7.33 (d, 2H, J = 8.1 Hz), 7.83 (d, 2H, J = 8.3 Hz), 8.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 12.7, 21.6, 23.0, 127.8, 129.6, 134.7, 135.6, 144.2, 158.4, 174.1; HRMS (ESI) calcd for $C_{13}H_{18}NO_2S$ (M + H^+) 252.1058, found 252.1059.

***N*-((*E*)-2-Ethylhex-2-enylidene)-4-methylbenzenesulfonamide (11b).** The general procedure described above was followed when 1.6 mL of butyraldehyde **7b** (1.3 g, 17.52 mmol) was reacted with 2.0 g of *p*-toluenesulfonamide (11.68 mmol) to afford **11b** (2.18 g, 67% yield) as a white solid: mp 53−55 °C; R_f 0.42 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3439, 2958, 2870, 1631, 1570, 1462, 1398, 1317, 1288, 1237, 1210, 1164, 1085, 1042, 915, 863, 815, 778, 707, 673, 628, 584, 561, 543, 467; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.93 (m, 6H), 1.45 (q, 2H, J = 7.3 Hz), 2.24−2.32 (m, 4H), 2.36 (s, 3H), 6.40 (t, 1H, J = 7.3 Hz), 7.20−7.29 (m, 2H), 7.74−7.77 (m, 2H), 8.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 13.8, 18.6, 21.6, 21.9, 31.3, 127.7, 129.6, 135.8, 141.2, 144.1, 156.8, 173.6; HRMS (ESI) calcd for $C_{15}H_{22}NO_2S$ (M + H^+) 280.1371, found 280.1370.

Procedure for the Synthesis of *N*-Tosylalkenyl-Substituted Piperidines. To a solution of diisopropylamine (0.08 mL, 0.55 mmol) in 2.0 mL of dry THF was added 2.0 M *n*-BuLi (0.28 mL, 0.55 mmol) at 0 °C and the mixture stirred for 30 min. The color of the solution changed to yellow, the temperature was dropped to −50 °C, compound (*E*)-**1a** (100.0 mg, 0.46 mmol) dissolved in 1.0 mL of dry THF was added slowly, and the mixture was stirred for 1 h to allow the formation of enolate. Then 2-alkenyl-*N*-tosylaldimine **11a**,**b** (0.46 mmol), dissolved in 1.0 mL of dry THF, was added, and the mixture was stirred for an additional 6−6.5 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 3−4% ethyl acetate in petroleum ether as eluent to afford the pure piperidines **12a**,**b** as a white solid. All these compounds exist in enol form as indicated by ^{1}H NMR spectra and crystal structure.

Ethyl 4-Hydroxy-6(*E*)-(pent-2-en-2-yl)-2-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (12a). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 115.0 mg of **11a** (0.46 mmol) at −50 °C for 6 h to afford **12a** (125.0 mg, 58% yield) as a white solid: mp 154−156 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3443, 3059, 2960, 2930, 2872, 1656, 1621, 1492, 1451, 1408, 1344, 1297, 1233, 1184, 1162, 1094, 1026, 993, 963, 894, 809, 749, 701, 687, 655, 627, 561; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.6 Hz), 0.95−1.01 (m, 6H), 1.48−1.55 (m, 1H), 1.63−1.71 (m, 1H), 2.07 (dd, 1H, J = 7.3, 18.4 Hz), 2.39−2.46 (m, 4H), 4.01−4.16 (m, 2H), 4.38 (d, 1H, J = 6.9 Hz), 4.95−5.01 (m, 1H), 6.07 (s, 1H), 7.13−7.21 (m, 3H), 7.25−7.29 (m, 4H), 7.73 (d, 2H, J = 8.5 Hz), 12.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 14.0, 14.2, 21.3, 21.7, 28.4, 53.5, 56.0, 60.7, 96.4, 126.8, 127.1, 127.3, 128.7, 129.7, 129.9, 132.4, 137.4, 140.0, 143.8, 170.6, 170.9; HRMS (ESI) calcd for $C_{26}H_{32}NO_5S$ (M + H^+) 470.2001, found 470.2004.

Ethyl 6-(*E*)-Hept-3-en-3-yl)-4-hydroxy-2-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (12b). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 128.0 mg of **11b** (0.46 mmol) at −50 °C for 6.5 h to afford **12b** (128.0 mg, 56% yield) as a white solid: mp 142−144 °C; R_f 0.46 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3426, 3059, 2963, 2929, 1660, 1606, 1495, 1459, 1427, 1403, 1368, 1344, 1295, 1223, 1161, 1095, 1029, 987, 812, 751, 703, 656, 590, 560, 536, 457; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (t, 3H, J = 7.5 Hz), 0.82 (t, 3H, J = 7.5 Hz), 0.99 (t, 3H, J = 7.8 Hz), 1.10−1.31 (m, 3H), 1.43−1.54 (m, 2H), 1.59−1.68 (m, 1H), 2.15 (dd, 1H, J = 7.4, 18.3 Hz), 2.34−2.40 (m, 1H), 2.43 (s, 3H), 4.01−4.16 (m, 2H), 4.52 (d, 1H, J = 7.5 Hz), 4.90−4.96 (m, 1H), 6.04 (s, 1H), 7.11 −7.20 (m, 3H), 7.23−7.32 (m, 4H), 7.74 (d, 2H, J = 8.0 Hz), 12.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8, 13.9, 14.0, 20.1, 21.6, 22.2, 28.4, 29.7, 52.6, 53.1, 53.2, 60.6, 96.3, 126.5, 127.0, 128.0, 128.1, 128.6, 129.8, 137.3, 138.7, 139.7, 143.7, 170.5, 170.9; HRMS (ESI) calcd for $C_{28}H_{36}NO_5S$ (M + H^+) 498.2314, found 498.2315.

Procedure for the Synthesis of *N*-Sulfinyl 2,6-Disubstituted Piperidines. To a solution of diisopropylamine (0.08 mL, 0.55 mmol) in 2.0 mL of dry THF was added *n*-BuLi 2.0 M) (0.28 mL, 0.55 mmol) at 0 °C and the mixture stirred for 30 min. The color of the solution changed to yellow, the temperature was dropped to −50 °C, compound (*E*)-**1a** (100.0 mg, 0.46 mmol) dissolved in 1.0 mL of dry THF was added, and the mixture was stirred for 1 h to allow the formation of enolate. Then 2-aryl-*N*-sulfinylaldimine **13a**−**d** (0.183 mmol) dissolved in 1.0 mL of dry THF was added and the mixture stirred for an additional 8−10 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 8% ethyl acetate in petroleum ether to afford the pure piperidines **14a**−**d**. All these compounds exist in enol form as indicated by ^{1}H NMR spectra and crystal structure.

4-Hydroxy-2,6-diphenyl-1-(toluene-4-sulfinyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (14a). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 44.6 mg of **13a** (0.18 mmol) at −50 °C for 8.0 h to afford **14a** (47.0 mg, 55% yield) as a white solid: mp 120−122 °C; R_f 0.58 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -73.3$ (*c* 0.685 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3446, 2922, 2853, 1655, 1493, 1453, 1404, 1301, 1264, 1225, 1182, 1071, 1018, 910, 813, 754, 695, 570, 469, 432; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.3 Hz), 2.37 (s, 3H), 2.73 (dd, 1H, J = 5.4, 17.2 Hz), 2.97 (dd, 1H, J = 7.3, 17.2 Hz), 4.02−4.15 (m, 2H), 4.95−5.0 (m, 1H), 5.58 (s, 1H), 6.51 (d, 2H, J = 7.3 Hz), 6.80−6.84 (m, 2H), 6.87−6.92 (m, 1H), 7.14−7.24 (m, 5H), 7.29 (d, 2H, J = 6.9 Hz), 7.46 (d, 2H, J = 8.0 Hz), 12.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.3, 34.8, 51.5, 59.1, 60.6, 101.2, 125.8, 125.9, 127.2, 127.3, 127.6, 127.8, 128.4, 129.3, 140.1, 140.4, 141.6, 142.6, 170.2, 170.3; HRMS (ESI) calcd for $C_{27}H_{28}NO_4S$ (M + H^+) 462.1739, found 462.1735.

4-Hydroxy-6-(4-nitrophenyl)-2-phenyl-1-(toluene-4-sulfinyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (14b). The general procedure described above was followed when the enolate of (*E*)-**1a** (100.0 mg, 0.46 mmol) reacted with 52.8 mg of **13b** (0.183 mmol) at −50 °C for 8.5 h to afford **14b** (53.0 mg, 58% yield) as a light yellow solid: mp 148−152 °C; R_f 0.44 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = +23.3$ (*c* 0.85 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3446, 2922, 1656, 1518, 1449, 1403, 1382, 1347, 1298, 1224, 1169, 1094, 1075, 988, 889, 850, 814, 752, 702, 461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.1 Hz), 2.44 (s, 3H), 2.65 (dd, 1H, J = 6.4, 17.8 Hz), 2.86 (dd, 1H, J = 4.6, 17.8 Hz), 4.0−4.16 (m, 2H), 4.97−5.03 (m, 1H), 5.64 (s, 1H), 6.5 (d, 2H, J = 7.6 Hz), 6.75−6.93 (m, 3H), 7.25−7.35 (m, 4H), 7.58 (d, 2H, J = 7.8 Hz), 7.89 (d, 2H, J = 8.5 Hz), 12.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 32.2, 53.2, 55.9, 60.8, 100.2, 123.2, 125.6, 126.4, 127.1, 127.3, 128.8, 129.8, 140.2, 141.0, 142.3, 146.9, 147.0, 169.5, 170.1; HRMS (ESI) calcd for $C_{27}H_{27}N_2O_6S$ (M + H^+) 507.1589, found 507.1595.

6-(4-Chlorophenyl)-4-hydroxy-2-phenyl-1-(toluene-4-sulfinyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester (14c). The general procedure described above was followed when the enolate of (*E*)-**1a** (100 mg, 0.46 mmol) reacted with 50.8 mg of **13c** (0.183 mmol) at −50 °C for 10 h to afford **14c** (56 mg, 62% yield) as a white solid: mp 164−168 °C; R_f 0.52 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -32.8$ (*c* 0.75 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3421, 3030, 2977, 2925, 1958, 1717, 1658, 1492, 1453, 1404, 1368, 1301, 1260, 1227, 1180, 1089, 1015, 983, 910, 815, 701, 628, 518; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.1 Hz), 2.33 (s, 3H), 2.61 (dd, 1H, J = 5.8, 17.6 Hz), 2.80 (dd, 1H, J = 6.1, 17.6 Hz), 3.93−4.08 (m, 2H), 4.83−4.89 (m, 1H), 5.51 (s, 1H), 6.41 (d, 2H, J = 7.8 Hz), 6.74−6.80 (m, 2H), 6.83−6.89 (m, 1H), 7.01−7.10 (m, 4H), 7.16 (d, 2H, J = 8.1 Hz), 7.43 (d, 2H, J = 8.3 Hz), 12.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.5, 33.8, 52.2, 57.5, 60.8, 100.8, 125.9, 126.1, 127.3, 127.4, 128.5, 129.3, 129.6, 133.4, 138.7, 140.2, 141.9, 142.0, 170.1, 170.3; HRMS (ESI) calcd for $C_{27}H_{27}ClNO_4S$ (M + H^+) 496.1349, found 496.1349.

Procedure for the Synthesis of Chiral *N*-Tosyl 2,6-Disubstituted Piperidines from *N*-Sulfinyl 2,6-Disubstituted Piperidines. To a solution of **14c**,**d** in 1.5 mL of dry CH_2Cl_2 was added *m*-chloroperbenzoic acid and the mixture stirred at room temperature for 2−3 h. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2.0 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 8% ethyl acetate in petroleum ether to afford (2*R*,6*R*)-**6d**,**f** as a white solid.

(2*R*,6*R*)-Ethyl-6-(4-chlorophenyl)-4-hydroxy-2-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate [(2*R*,6*R*)-6d]. The general procedure described above was followed when the piperidine **14c** (25 mg 0.05 mmol) was reacted with *m*-chloroperbenzoic acid (17.5 mg, 0.1 mmol) at room temperature for 2.5 h to afford (2*R*,6*R*)-**6d** (16.8 mg, 65% yield) as a white solid: $[\alpha]^{25}_D = -29.8$ (*c* 0.275 in $CHCl_3$). For detailed spectral data, see compound **6d**.

(2*R*,6*R*)-Ethyl 4-Hydroxy-6-(4-methoxyphenyl)-2-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate [(2*R*,6*R*)-6f]. The general procedure described above was followed when the piperidine **14d** (25 mg 0.05 mmol) was reacted with *m*-chloroperbenzoic acid (17.5 mg, 0.1 mmol) at room temperature for 3.0 h to afford (2*R*,6*R*)-**6f** (17 mg, 65% yield) as a white solid: $[\alpha]^{25}_D = -12.9$ (*c* 0.255 in $CHCl_3$). For detailed spectral data, see compound **6f**.

Procedure for the Synthesis of *N*-Tosyl 2,6-Disubstituted Piperidines from 1c. To a solution of diisopropylamine (0.08 mL, 0.54 mmol) in 2.0 mL of dry THF was added 2.0 M *n*-BuLi (0.27 mL, 0.54 mmol) at 0 °C and the mixture stirred for 30 min under argon atmosphere. The color of the solution changed to yellow, the temperature was dropped to −50 °C, compound **1c** (*E*-*Z*) (100.0 mg, 0.45 mmol) dissolved in 1.0 mL dry THF was added slowly, and the mixture was stirred for 1 h to allow the formation of enolate. Then 2-phenyl-*N*-tosylaldimine **3a** 117.0 mg (0.45 mmol), dissolved in 1.5 mL of dry THF, was added and the mixture stirred for an additional 6 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 5% ethyl acetate in petroleum ether to afford the pure piperidines **18a**,**b** as a white solid. These compounds exist in enol form as indicated by the ^{1}H NMR spectrum and crystal structure.

Ethyl 2-Cyclohexyl-4-hydroxy-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (18a). The general procedure described above was followed when the enolate of (*E*)-**1c** (100.0 mg, 0.45 mmol) reacted with 117.0 mg of **3a** (0.45 mmol) at −50 °C for 6 h to afford **18a** (132.0 mg, 61% yield) as a white solid: mp 132−133 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3432, 2922, 2852, 1649, 1619, 1494, 1451, 1428, 1408, 1332, 1277, 1222, 1163, 1090, 1074, 1026, 989, 947, 896, 877, 818, 750, 737, 675, 654, 607, 561, 544, 462; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83−1.13 (m, 6H), 1.30 (t, 3H, J = 7.3 Hz), 1.52−1.65 (m, 4H), 1.73−1.79 (m, 1H), 2.32 (s, 3H), 2.46 (dd, 1H, J = 6.9, 16.8 Hz), 2.66 (dd, 1H, J = 10.7, 16.8 Hz), 4.0−4.21 (m, 2H), 4.57 (d, 1H, J = 10.7 Hz), 4.64−4.69 (m, 1H), 7.13 (d, 2H, J = 8.1 Hz), 7.18−7.24 (m, 1H), 7.28−7.35 (m, 4H), 7.57 (d, 2H, J = 8.4 Hz), 11.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.5, 26.0, 26.2, 26.5, 30.0, 31.2, 34.9, 43.3, 58.3, 58.5, 60.6, 100.4, 126.4, 127.4, 127.6, 128.6, 129.3, 135.4, 143.2, 143.5, 169.9; HRMS (ESI) calcd for $C_{27}H_{34}NO_5S$ (M + H^+) 484.2157, found 484.2157.

Ethyl 2-Cyclohexyl-4-hydroxy-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (18b). The general procedure described above was followed when the enolate of (*Z*)-**1c** (100.0 mg, 0.45 mmol) reacted with 117.0 mg of **3a** (0.45 mmol) at −50 °C for 6 h to afford **18b** (141.5 mg, 65% yield) as a white solid: mp 145−147 °C; R_f 0.45; (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3442, 2928, 2851, 1640, 1497, 1452, 1403, 1356, 1337, 1323, 1262, 1229, 1217, 1182, 1151, 1091, 1059,

1030, 1010, 937, 895, 862, 811, 766, 735, 724, 696, 659, 601, 584, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.19 (m, 6H), 1.32 (t, 3H, J = 7.1 Hz), 1.60−1.81 (m, 4H), 1.96−2.06 (m,1H), 2.25 (s, 3H), 2.62 (dd, 1H, J = 5.4, 17.4 Hz), 3.07 (dd, 1H, J = 9.3, 17.4 Hz), 4.17−4.32 (m, 2H), 4.85−4.95 (m, 2H), 6.88 (d, 2H, J = 8.5 Hz), 7.0−7.12 (m, 7H), 12.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.3, 26.2, 26.5, 26.6, 30.0, 31.0, 33.0, 44.7, 54.5, 58.0, 60.8, 100.9, 126.7, 127.6, 127.9, 128.4, 128.6, 137.1, 139.4, 142.1, 170.8, 170.9; HRMS (ESI) calcd for $C_{27}H_{34}NO_5S$ ($M + H^+$) 484.2157, found 484.2157.

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Supporting Information Available: X-ray crystallographic data of **6a**,**e**,**j**, **12a**, **14c**, and **18a**,**b**, copies of ^{1}H and ^{13}C spectra for all compounds, and HPLC chromatograms for er determination. This material is available free of charge via the Internet at http://pubs.acs.org