DOI: 10.1002/adsc.201000701

An Easy, Stereoselective Synthesis of Hexahydroisoindol-4-ones under Phosphine Catalysis

Deepti Duvvuru,[a] Jean-François Betzer,[a,*] Pascal Retailleau,[a] Gilles Frison,[b] and Angela Marinetti[a,*]

[a] Institut de Chimie des Substances Naturelles, CNRS UPR 2301–1, av. de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
Fax: (+33)-01-6907-7247; phone: (+33)-01-6982-3036; e-mail: jean-francois.betzer@icsn.cnrs-gif.fr or angela.marinetti@icsn.cnrs-gif.fr

[b] Laboratoire des Mécanismes Réactionnels - CNRS UMR 7651, Ecole Polytechnique, Département de Chimie, 91128 Palaiseau Cedex, France

Received: September 9, 2010; Revised: November 19, 2010; Published online: February 16, 2011

Abstract: A new synthetic approach to hexahydroisoindol-4-ones is reported, based on the formal [3+2]cyclization reaction between *N*-arylsulfonylimines and cyclic conjugated dienes, under phosphine catalysis. Key substrates are 3-vinylcyclohex-2-enones with electron-withdrawing substituents (ester, amido, cyano, phosphoryl and keto groups) on the exocyclic double bond, which afford the three-atom synthons for the construction of the pyrroline ring. Total *syn* stereoselectivity is observed in these annulations. The scope of the reaction has been demonstrated and mechanistic issues are considered, based on deuteration experiments and density function theory (DFT) calculations.

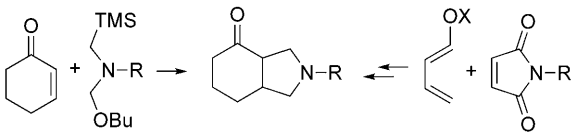
Keywords: [3+2]annulations; conjugated dienes; hexahydroisoindolones; imines; phosphine organocatalysis

Introduction

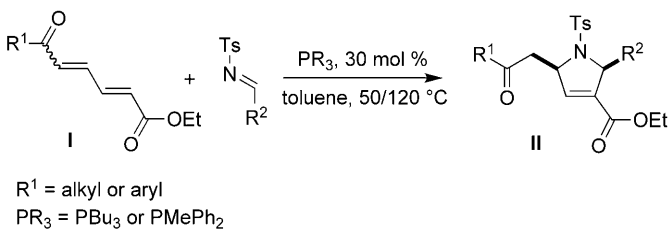
Isoindoline units are commonly found in biologically relevant compounds and drug candidates displaying a remarkable variety of activities.[1] The related perhydroisoindol-4-ones have also found applications as core scaffolds or synthetic intermediates in medicinal chemistry.[2] Common synthetic strategies (Scheme 1) toward saturated fused bicyclic amines of this class mainly involve the 1,3-dipolar cycloaddition of azomethine ylides on suitable cyclic olefins[3] or Diels–Alder type reactions on maleimide.[4,5]

A new, alternative and practical synthesis of hexahydro-*4H*-isoindol-4-one derivatives is reported hereafter, based on phosphine catalyzed [3+2]cyclizations[6] which involve imines and dienes as the two-atom and three-atom components, respectively. The method has been unexpectedly brought to light while expanding the scope of the recently disclosed reaction between electron-poor conjugated dienes and imines, under phosphine catalysis, shown in Scheme 2.[7] In this reaction, starting from acyclic conjugated dienes properly activated by electron-withdrawing groups on both ends, 3-pyrrolines were produced.[8] The cyclization took place selectively on the double bond substituted by the ester function, according to the formal activation of this bond by the nucleophilic phosphine.

As a logical extension of this previous work, the same strategy has now been applied to conjugated dienes where one of the double bonds is embedded in a cyclic moiety. These experiments have allowed an efficient access to the hexahydroisoindol-4-one scaffolds **3** to be implemented.



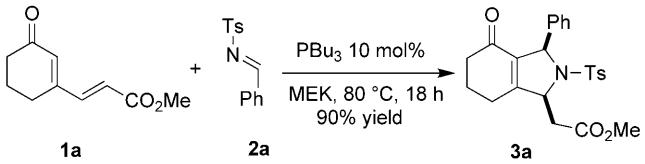
Scheme 1. Synthetic approaches to perhydroisoindol-4-one scaffolds.



Scheme 2. Synthesis of pyrrolines from conjugated dienes and imines under phosphine catalysis.[7]

Results and Discussion

With the purpose of expanding the scope of the phosphine-promoted annulation reactions between imines and conjugated dienes shown in Scheme 2,[7] we have considered 3-(2-methoxycarbonylvinyl)-2-cyclohexenone **1a**[9] as a model substrate for initial studies. Diene **1a** has been reacted with *N*-tosyl-benzaldimine in the presence of trivalent phosphines as nucleophilic catalysts (Scheme 3).

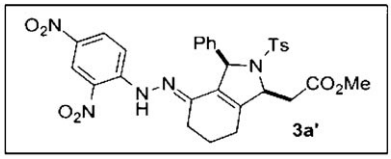


1a 2a 3a

Scheme 3. Phosphine promoted annulation between the cyclic diene **1a** and imine **2a**.

A clean reaction took place indeed, leading to the bicyclic pyrroline **3a**, whose formation has been optimized by a rapid screening of catalysts [PBu_3, PMe_3, PMe_2Ph, $PMePh_2$, PPh_3, $P(i\text{-}Bu)_3$] and reaction conditions. The optimized conditions include the use of PBu_3 as the catalyst, a 2:1 imine:diene ratio, polar solvents (methyl ethyl ketone or *t*-BuOH) and a reaction temperature of 80 °C. In MEK, with a 10 mol% amount of the phosphorus catalyst, total conversion could be attained after 18 h.

The molecular structure of **3a** has been assigned at first by NMR and unambiguously established then by X-ray crystallography on the corresponding hydrazone **3a′** (Figure 1).[10] NMR and structural data indicate that the reaction affords exclusively the *syn* isomer of the bicyclic fused pyrroline, with total chemo- and stereoselectivity.



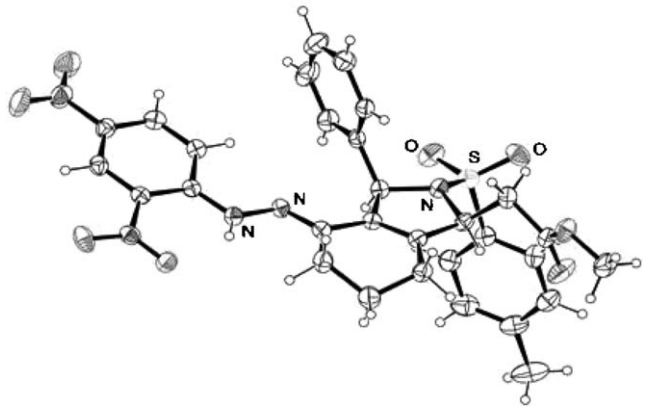


Figure 1. X-ray crystal structure of hydrazone **3a′**.

The outcome of this cyclization reaction highlights a striking chemodivergent behaviour of the cyclic diene **1a** with respect to the acyclic analogue **I**, as far as cyclization takes place on the enone function of **1a** while it was shown to take place on the enoate function of **I** (Scheme 2). This result poses some mechanistic concerns which will be discussed briefly in the final section of this paper.

Since a variety of hexahydroisoindol-4-ones might be easily available from simple starting materials following the synthetic strategy typified in Scheme 1, we next examined the scope of this catalytic process. Representative results are depicted in Table 1. The cyclization reaction can be performed with tosylimines bearing substituted aryls, heteroaryls (entry 3) and alkyl groups (entry 7). It also tolerates *p*-chloro- and *p*-nitrophenylsulfonyl activating groups on the nitrogen atom (entries 8 and 9), while *N*-DPP imines failed to react. Most reactions take place at 80 °C with a 10 mol% amount of PBu_3, but in some cases it may be advantageous to increase the catalyst amount or the temperature in order to increase the conversion rates. Both methyl ethyl ketone (MEK) and *t*-BuOH are suitable solvents. According to NMR analyses, the crude final mixtures contain **3** and, possibly, some residual starting material, with only minor amounts of side products.

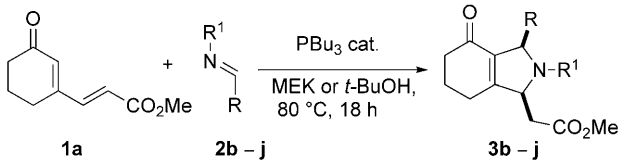
The fused bicyclic pyrrolines **3b–j** were obtained as single isomers which have been assigned as the *syn* isomers by analogy to **3a**, based on their typical ^{1}H NMR pattern. The two NCH units of **3a** display signals at $\delta = 5.6$ (d, $J = \sim 1.2$ Hz, NCHAr) and 5.0 ppm, while the chemical shifts of the CH_2-CO_2Me units are at about 3 ppm (AB system with $^2J_{H,H} = \sim 16$ Hz, $^3J_{H,H} = \sim 4$ and ~ 8 Hz).

Further efforts have been directed then toward modulation of the withdrawing group of the diene moiety (Scheme 4). Dienes **5a–e** bearing keto, amido, cyano and diethylphosphoryl functions on the external double bond, have been prepared by Heck reactions from either 3-tosyloxy- or 3-bromo-2-cyclohexenones and suitably functionalized olefins. They have been reacted then with *N*-tosylbenzaldimine in the presence of PBu_3 in MEK.

Compared to **1a**, the new dienic substrates **5** displayed lower reactivity, nevertheless the desired hexahydroisoindol-4-ones **6** could be obtained in moderate to good yields for reactions carried out at 100 °C, with about 30 mol% catalyst.[11] In these reactions also, the final products were isolated as single isomers.

In additional experiments, variation of the ring size of the dienic substrate has been attempted by considering the five-membered cyclic diene **7** as a possible reaction partner. Diene **7** has been prepared by Heck

Table 1. Phosphine-promoted synthesis of the hexahydroisoindol-4-ones **3**: variations of the imine partner.



Entry	Imine	R	R^1	PBu_3 (%)	Product	Yield [%][a]
1	**2b**	4-Cl-C_6H_4	Ts	10	**3b**	93
2	**2c**	4-CF_3-C_6H_4	Ts	30	**3c**	78
3	**2d**	2-thienyl	Ts	10	**3d**	76
4	**2e**	4-MeO-C_6H_4	Ts	30	**3e**	82[b]
5	**2f**	1-naphthyl	Ts	10	**3f**	83
6	**2g**	*p*-NO_2-C_6H_4	Ts	30	**3g**	47[c]
7	**2h**	*i*-Pr	Ts	30	**3h**	71[d]
8	**2i**	Ph	4-Cl-$C_6H_4SO_2$	10	**3i**	82
9	**2j**	Ph	4-NO_2-$C_6H_4SO_2$	10	**3j**	44

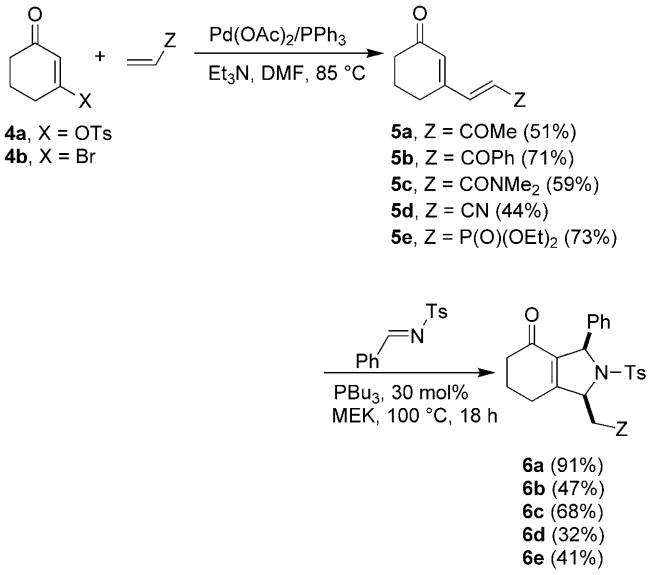
[a] *Reaction conditions:* reactions have been performed at a 0.3 mmol scale, under argon, in degassed MEK (1 mL, entries 1–5 and 8) or *t*-BuOH (1 mL, entries 6, 7, 9); diene:imine ratio = 1:1.5, unless otherwise stated.
[b] Reaction temperature: 100 °C.
[c] Diene:imine ratio = 1:2.
[d] Diene:imine ratio = 1:3.

reaction between methyl acrylate and 3-iodocyclopent-2-enone,[12] with $Pd(OAc)_2/Ph_2P(CH_2)_3PPh_2$ as the catalyst. In the usual conditions, the reaction of **7** with *N*-tosylbenzaldimine failed to give the expected pyrroline displaying a bicyclo-[3.3.0] scaffold. It produced however the aza-Morita–Baylis–Hillman adduct **8** in 70% yield.

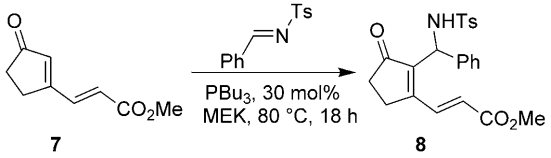
The aza-MBH reaction takes place selectively on the enone function, despite the fact that this will involve formal activation of a trisubstituted double bond by the phosphorus nucleophile. As far as we know, this is an unprecedented example of phosphine-promoted an aza-MBH reaction on a β-substituted cyclic enone.

In summary, the results in Scheme 5 show that, in the case of cyclopentenone derivatives, the annulation reaction is no longer competitive with the direct elimination of the phosphine leading to the classical aza-MBH adduct. Therefore, the application field of our method is restricted so far to the synthesis of the [4.3.0] bicyclic moiety of isoindolinones.

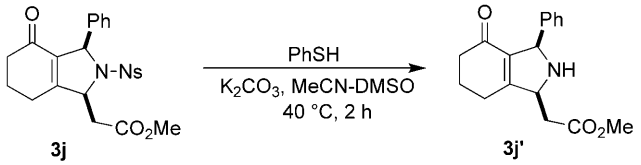
Finally, in order to expand the synthetic utility of the method, we have checked the feasibility of nitrogen deprotection in the final bicyclic product. To this end, we have considered the *N*-nosyl-protected tetrahydroisoindolone **3j**, since mild deprotection protocols are known for the nosyl group. The nosyl group could be removed actually by reaction of **3j** with thiophenol in the presence of sodium carbonate (Scheme 6).[13]



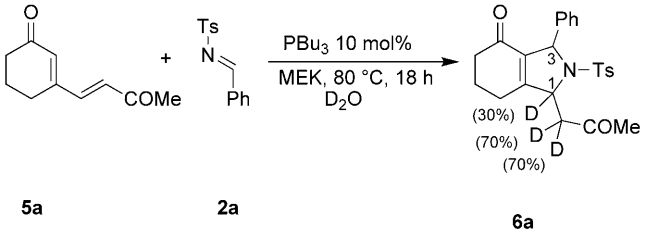
Scheme 4. Synthesis of hexahydroisoindol-4-ones with various functional groups tethered to the 1-position.



Scheme 5. Aza-Morita-Baylis–Hillman type reaction of vinylcyclopentenone **7** and *N*-tosylbenzaldimine.



Scheme 6. Removal of the nosyl protecting group from isoindoline **3j**.

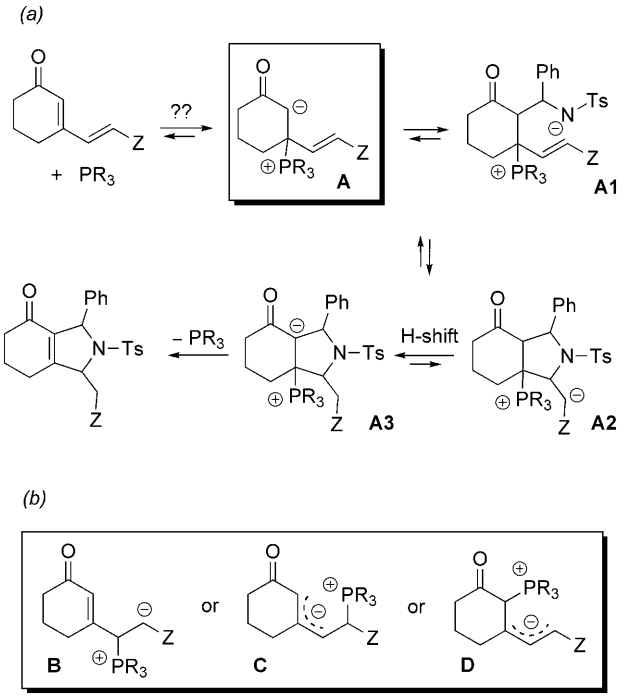


Scheme 8. Cyclization reaction in the presence of D_2O.

The final secondary amine has been isolated from the crude reaction mixture, in pure form and good yield (66%), by extraction in acid solution. NMR data show that the bicyclic pyrroline ring is retained during the deprotection procedure.

Mechanistic Considerations

From a mechanistic point of view, the most straightforward pathway for building the tetrahydroisoindolines **3** (or **6**) would involve addition of the phosphorus nucleophile to the intracyclic double bond of **1** or **5** (path *a* in Scheme 7), followed by nucleophilic addition of ***A*** to the imine. Intermediate **A1** should undergo then an intramolecular Michael-type addition leading to **A2**. A formal [1,4]-proton shift will then convert **A2** into **A3** and create a negative charge β to the phosphorus centre. The phosphine elimination step achieves the cyclization process. This mechanism implies the preferential activation of the internal, trisubstituted double bond of the starting diene *vs.* activation of the disubstituted enoate function *via* intermediate ***B*** (Scheme 7b). This is rather unexpected, especially when considering that the related phosphine-promoted aza-Morita–Baylis–Hillman reactions seldom apply to β-substituted Michael acceptors.[14,15]



Scheme 7. *(a)* A straightforward mechanism for the annulation reaction. *(b)* Alternative zwitterionic intermediates generated by phosphine addition to the conjugated dienes.

Therefore, in order to get additional information on possible reaction intermediates, the cyclization between **5a** and **2a** has been performed in the presence of excess D_2O, as shown in Scheme 8. Since H-shifts are known to be mediated by traces of water,[16] deuterium is expected to be incorporated on all positions involved in H-shift processes.

The sample of **6a** isolated from this experiment contains a significant amount of deuterium (70%) at the methylene carbon α to the COMe function. This was fully anticipated, due to the postulated formation of intermediate **A2**. However, deuterium has been partially incorporated also at the C-1 carbon of **6a** (30%) while the C-3 moiety contains only protons. The mechanism shown in Scheme 7a does not account, by itself, for the observed deuterium distribution, since it does not involve H-exchanges at the C-1 carbon.

Therefore, less straightforward mechanisms cannot be excluded so far, which might involve initial addition of the phosphorus catalyst to other sites of the dienic moiety.

According to Hückel and quantum chemical calculations, the LUMO orbital of conjugated dienes such as **1a** or **5a** is distributed along the dienic unit, with roughly identical coefficients on the four atoms (Figure 2). Consequently, the zwitterionic species ***B***, ***C*** and ***D*** (Scheme 7b) might also be formed by addition of the nucleophilic phosphine to the α, γ and δ positions of the dienic ketone. They might enter a catalytic cycle or, alternatively, their reversible formation might induce H/D exchange reactions accounting for the observed D-distribution in the final product **6a** (Scheme 8).

The reversible addition of tributylphosphine to the diene has been evidenced by the H/D exchange experiment shown in Scheme 9.

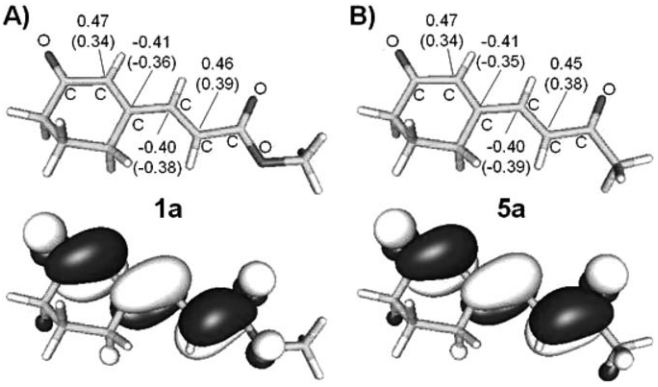
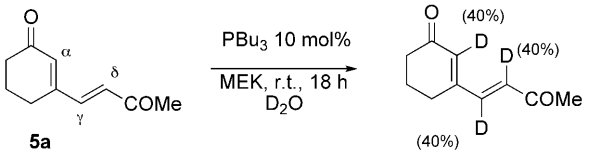


Figure 2. LUMO coefficients for the dienic carbon atoms at the HF and Hückel (in brackets) levels (*top*) and qualitative view of the LUMO at the DFT level (*bottom*) for A) **1a** and B) **5a**.



Scheme 9. PBu_3-promoted, H/D exchange reactions.

When **5a** was stirred at room temperature in the presence of PBu_3 and D_2O, deuterium has been incorporated in comparable amounts on the α, γ and δ carbons of the starting dienic unit.

Thus, experimental data and calculations support the hypothesis of an initial, reversible addition of the phosphorus nucleophile to various positions of the dienic substrate generating different zwitterionic adducts. The reaction outcome will be determined then at a later step of the catalytic cycle.

Additional studies are required to enlucidate the precise mechanism of these cyclization reactions.

Conclusions

This work demonstrates that the phosphine-mediated organocatalytic annulations between 3-vinylcyclohexenones and *N*-arylsulfonylimines produce hexahydroisoindol-4-ones with various functional groups connected to the C-1 carbon by a CH_2 spacer. This represents a new, easy and stereoselective access to isoindoline derivatives with an unprecedented substitution scheme. Insights into the reaction mechanism have been obtained from deuteration experiments and DFT calculations which demonstrate the reversible addition of the phosphorus catalyst to the dienic unit.

The method proved unsuitable for the direct synthesis of the analogous 2-azabicyclo[3.3.0]units from cyclopentenone derivatives. Cyclic substrates with different ring sizes are now considered in ongoing studies.

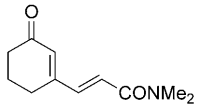
Experimental Section

Synthesis of the Conjugated Dienes 1, 5 and 7 *via* Heck Reactions

(*a*) Dienes **1a** and **5a**, **c**, **e** have been prepared from tosylate **4a** according to the reported method.[9]

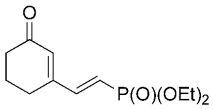
Representative procedure: A mixture of tosylate **4a** (4.0 g, 15 mmol), a suitable olefin $H_2C{=}CHZ$ (22 mmol), Et_3N (3.3 mL, 24 mmol), $Pd(OAc)_2$ (50.6 mg, 0.22 mmol) and PPh_3 (59 mg, 0.22 mmol) in degazed *N*,*N*-dimethylacetamide (11 mL)/DMF (4.5 mL) was heated at 105 °C under argon for 24 h. The reaction mixture was routinely monitored by ^{1}H NMR. If needed, additional amounts of $Pd(OAc)_2/PPh_3$ were added to achieve total conversion of the starting tosylate.After aqueous work-up with 0.5 N HCl, the organic layer was washed with $NaHCO_3$ and water and evaporated to dryness. The final product was purified by column chromatography on silica gel.

(*E*)-*N*,*N*-Dimethyl-3-(3-oxocyclohex-1-enyl)acrylamide (5c)



Obtained in 59% yield (0.85 g, 4.4 mmol) from tosylate **4a** (2.0 g, 7.5 mmol) and *N*,*N*-dimethyl acrylamide (1.1 g, 11 mmol) (*Method a*). The final product was purified by column chromatography with ethyl acetate ($R_f = 0.2$) as the eluent. ^{1}H NMR ($CDCl_3$): $\delta = 7.27$ (d, $J = 15.6$ Hz, 1H), 6.69 (d, $J = 15.6$ Hz, 1H), 6.11 (s, 1H), 3.10 (s, 3H), 3.01 (s, 3H), 2.50–2.39 (m, 4H), 2.09–2.00 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 199.8$ (CO), 165.6 (CO-N), 154.5 (C), 141.9, 131.4, 123.5, 37.6 (Me), 37.4 (Me), 35.9, 25.1, 22.1.

(*E*)-Diethyl 2-(3-oxocyclohex-1-enyl)vinylphosphonate (5e)

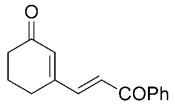


Obtained in 73% yield (1.3 g, 5.0 mmol) from tosylate **4a** (2.0 g, 7.5 mmol) and diethyl vinylphosphonate (1.1 g, 6.8 mmol). ^{1}H NMR ($CDCl_3$): $\delta = 7.12$ (dd, $J_{H,P} = 21.8$ Hz, $J = 17.4$ Hz, 1H), 6.11 (t, $J_{H,P} = \sim J_{H,H} = 17.7$ Hz, 1H), 6.06 (s, 1H), 4.06 (m, 4H), 2.40 (m, 4H, OCH_2), 2.03 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 6H, Me); ^{13}C NMR ($CDCl_3$): $\delta = 199.7$ (CO) 153.8 (d, $J = 23.5$ Hz), 147.9 (d, $J = 6.6$ Hz), 132.0 (=CH), 121.2 (d, $J = 189$ Hz, PCH), 62.1 (d, $J = 6.0$ Hz, OCH_2), 37.6, 24.5, 21.9, 16.3 (d, $J = 6.1$ Hz, Me); ^{31}P NMR ($CDCl_3$): $\delta =$ 17.

(*b*) Dienes **5b** and **5d** have been prepared by Heck reactions between 3-bromocyclohex-2-enone **4b** and the corre-

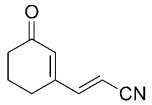
sponding olefins, following the same procedure. The reactions are completed after heating for 2 h at 85 °C.

(*E*)-3-(3-Oxo-3-phenylprop-1-enyl)cyclohex-2-enone (5b)



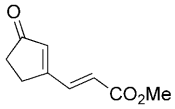
Obtained in 71% yield (0.92 g) from the bromide **4b** (1.0 g, 5.7 mmol) and phenyl vinyl ketone (1.0 g, 7.5 mmol). ^{1}H NMR ($CDCl_3$): $\delta = 7.90$ (d, $J = 7.0$ Hz, 2H), 7.53 (m, 1H), 7.4 (m, 2H), 7.39 (d, $J = 17$ Hz, 1H), 7.21 (d, $J = 17$ Hz, 1H), 6.20 (s, 1H), 2.54 (m, 2H), 2.43 (m, 2H), 2.06 (m, 2H).

(*E*)-3-(3-Oxocyclohex-1-enyl)acrylonitrile (5d)



Obtained in 44% yield (0.37 g) from bromide **4b** (1.0 g, 5.7 mmol) and acrylonitrile (0.40 mL, 6 mmol) after purification by column chromatography with an heptane-ethyl acetate gradient as the eluent. ^{1}H NMR ($CDCl_3$): $\delta = 7.13$ (d, $J = 16.5$ Hz, 1H), 6.13 (s, 1H), 5.75 (d, $J = 16.5$ Hz, 1H), 2.50–2.42 (m, 4H), 2.11 (m, 2H).

(c) (*E*)-Methyl 3-(3-oxocyclopent-1-enyl)prop-2-enoate (7)

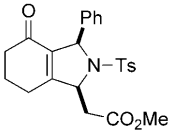


Diene **7** was prepared by the Heck reaction between 3-iodocyclopent-3-enone[12] and methyl acrylate. A mixture of 3-iodocyclopent-3-enone (0.50 g, 2.4 mmol), methyl acrylate (0.54 mL, 6 mmol), $Pd(OAc)_2$ (27 mg, 0.12 mmol), bis(diphenylphosphino)propane (25 mg, 0.06 mmol), Et_3N (0.65 mL, 4.8 mmol) in DMF (10 mL) was heated at 85 °C for 16 h. After aqueous workup with 0.5 N HCl, the organic layer was washed with $NaHCO_3$ and water and evaporated to dryness. The final product **7** was purified by column chromatography on silica gel with a heptane/ethyl acetate gradient ($R_f = 0.3$ in heptane/ethyl acetate 1:1); yield: 0.20 g (50%). ^{1}H NMR ($CDCl_3$): $\delta = 7.63$ (d, $J = 15.9$ Hz, 1H), 6.30 (d, $J = 15.9$ Hz, 1H), 6.29 (s, 1H), 3.78 (s, 3H), 2.7 (m, 2H), 2.49 (m, 2H);^{13}C NMR ($CDCl_3$): $\delta = 208.8$ (CO), 168.3 (CO_2Me), 166.2 (C), 138.6 (CH), 136.1 (CH), 125.0 (CH), 52.3 (OMe), 35.1 (CH_2), 27.0 (CH_2).

Phosphine-Promoted Cyclization Reactions

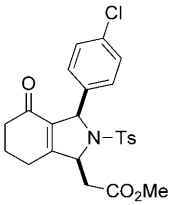
General procedure: PBu_3 (25–75 μmol) was added to a mixture of diene (0.25 mmol) and imine (0.50 mmol) in methyl ethyl ketone (or *t*-BuOH) (1 mL) under argon. The mixture was heated overnight (18 h) at the given temperature (see Scheme 3, 4 and Table 1). Conversion rates were determined on the crude mixture by ^{1}H NMR, with 1,3,5-trimethoxybenzene as the internal standard. After evaporation of the solvent, the final product was purified by column chromatography on silica gel.

Methyl 2-(3-Phenyl-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)acetate (3a)



Compound **3a** was obtained in 90% yield (98 mg) after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.66$ (d, $J = 8.2$ Hz, 2H), 7.3–7.2 (7H), 5.61 (d, $J = 1.2$ Hz, 1H, N-CHPh), 5.03 (br, m, NCH), 3.74 (s, 3H, OMe), 3.17 (dd, $J =$ 15.9 and 4.0 Hz, 1H, CH_2CO_2Me), 2.93 (dd, $J = 15.9$ and 7.9 Hz, 1H, CH_2CO_2Me), 2.42 (s, Me), 2.4–2.2 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 194.4$ (CO), 170.7 (CO_2Me), 158.5 (*C*=C-CO), 144.0 (C), 139.9 (C), 135.0 (C), 134.4 (C), 129.8, 127.8, 127.7, 127.6, 68.2 (NCHPh), 65.6 (NCH), 52.1 (OMe), 40.1 (CH_2CO_2Me), 37.7 (CH_2CO), 23.6, 22.9, 21.5 (Me); HR-MS (ESI): $m/z = 462.1360$, calcd. for $C_{24}H_{25}NO_5S$ $[M+Na]^+$: 462.1351; IR (neat): $\nu = 1732$, 1673 cm^{-1}.

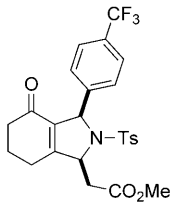
Methyl 2-[3-(4-Chlorophenyl)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3b)



Compound **3b** was obtained in 93% yield (110 mg) after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.65$ (d, $J = 8.0$ Hz, 2H), 7.3–7.2 (6H), 5.55 (d, $J = 1.2$ Hz, 1H, N-CHAr), 5.0 (br, m, NCH), 3.74 (s, 3H, OMe), 3.16 (dd, $J =$ 16.0 and 4.0 Hz, 1H, CH_2CO_2Me), 2.95 (dd, $J = 15.9$ and 8.0 Hz, 1H, CH_2CO_2Me), 2.43 (s, Me), 2.4–2.2 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 194.3$ (CO), 170.6 (CO_2Me), 158.8 (*C*=C-CO), 144.2 (C), 138.5 (C), 134.7 (C), 134.1 (C), 134.2 (C), 133.6 (C), 129.8, 129.0, 128.3, 127.8, 67.5 (NCHAr), 65.5 (NCH), 52.1 (OMe), 39.9 (CH_2CO_2Me), 37.7 (CH_2CO), 23.6, 22.9, 21.5 (Me); HR-MS (ESI): $m/z =$ 496.0950, calcd. for $C_{24}H_{24}ClNO_5S$ $[M+Na]^+$: 496.0961; IR (neat): $\nu = 1732$, 1675 cm^{-1}.

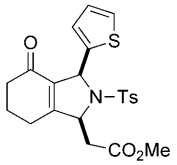
Methyl 2-{4-Oxo-2-tosyl-3-[4-(trifluoromethyl)-phenyl]-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl}acetate (3c)

Obtained in 78% yield after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.55$ (d, $J = 8.2$ Hz, 2H), 7.41 (d,



$J=8.5$ Hz, 2H), 7.34 (d, $J=8.5$ Hz, 2H), 7.20 (d, $J=8.2$ Hz, 2H), 5.58 (br, m, 1H, N-CHAr), 5.0 (br, m, 1H NCH), 3.70 (s, 3H, OMe), 3.13 (dd, $J=16.0$ and 4.1 Hz, 1H, CH_2CO_2Me), 2.97 (dd, $J=16.0$ and 7.4 Hz, 1H, CH_2CO_2Me), 2.36 (s, 3H, Me), 2.3–2.2 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=194.4$ (CO), 170.7 (CO_2Me), 159.2 (*C*=C-CO), 144.5 (C), 143.9 (C), 134.6 (C), 134.2 (C), 130.0 (C), 128.2, 128.0, 125.3, 125.2, 67.9 (NCHAr), 65.8 (NCH), 52.2 (OMe), 40.0 (CH_2CO_2Me), 37.8 (CH_2CO), 23.8, 23.0, 21.6 (Me); ^{19}F NMR ($CDCl_3$): $\delta=-62$ ppm; HR-MS (ESI): $m/z=530.1221$, calcd. for $C_{25}H_{24}F_3NO_5S$ $[M+Na]^+$: 530.1225; IR (neat): $\nu=1733$, 1674 cm^{-1}.

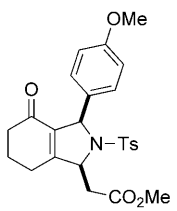
Methyl 2-[4-Oxo-3-(thiophen-2-yl)-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3d)



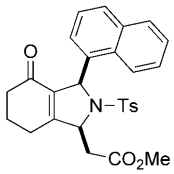
Obtained in 76% yield (85 mg) after purification with a heptane/ethyl acetate gradient ($R_f=0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta=7.60$ (d, $J=8.3$ Hz, 2H), 7.19 (d, $J=8.3$ Hz, 2H), 7.08 (dd, $J=5.2$ and 1.2 Hz, 1H), 6.99 (dd, $J=3.5$ and 1.2 Hz, 1H), 6.81 (dd, $J=5.2$ and 3.5 Hz, 1H), 5.88 (br, m, 1H, N-CHAr), 4.91 (br, m, 1H NCH), 3.63 (s, 3H, OMe), 3.01 (dd, $J=16.0$ and 4.2 Hz, 1H, CH_2CO_2Me), 2.80 (dd, $J=16.0$ and 8.0 Hz, 1H, CH_2CO_2Me), 2.33 (s, 3H Me), 2.3–2.2 (m, 4H), 2.0–1.8 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=194.4$ (CO), 170.7 (CO_2Me), 159.0 (*C*=C-CO), 144.4 (C), 144.2 (C), 135.0 (C), 134.7 (C), 130.0 (C), 127.8, 127.0, 126.6, 125.2, 65.5 (NCHAr), 63.5 (NCH), 52.2 (OMe), 40.4 (CH_2CO_2Me), 37.8 (CH_2CO), 23.9, 23.1, 21.7 (Me); HR-MS (ESI): $m/z=468.0918$, calcd. for $C_{22}H_{23}NO_5S_2$ $[M+Na]^+$: 468.0916; IR (neat): $\nu=1734$, 1676 cm^{-1}.

Methyl 2-[3-(4-Methoxyphenyl)-4-oxo-2-tosyl-2,3,4,5,6,7 -hexahydro-1*H*-isoindol-1-yl]acetate (3e)

Obtained in 82% yield (96 mg) after purification with a heptane/diethyl ether gradient ($R_f=0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta=7.62$ (d, $J=8.3$ Hz, 2H), 7.2–7.1 (m, 4H), 6.77 (d, $J=8.3$ Hz, 2H), 5.54 (br, m, 1H, N-CHAr), 4.95 (br, m, 1H NCH), 3.74 (s, 3H, OMe- Ar), 3.68 (s, 3H, OMe), 3.09 (dd, $J=15.9$ and 4.0 Hz, 1H, CH_2CO_2Me), 2.82 (dd, $J=15.9$ and 7.8 Hz, 1H, CH_2CO_2Me), 2.37 (s, 3H Me), 2.3–2.2 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=194.5$ (CO), 170.8 (CO_2Me), 159.3 (*C*=C-CO), 158.3 (C), 144.0 (C), 135.2 (C), 134.6 (C), 132.3 (C), 129.9, 128.8, 127.9, 113.7, 67.8 (NCHAr), 65.5 (NCH), 55.3 (OMe-Ar), 52.1 (OMe), 40.2 (CH_2CO_2Me), 37.8 (CH_2CO), 23.8, 23.0, 21.6 (Me); HR-MS (ESI): $m/z=470.1619$, calcd. for $C_{25}H_{28}NO_6S$ $[M+Na]^+$: 470.1637; IR (neat): $\nu=1732$, 1673 cm^{-1}.

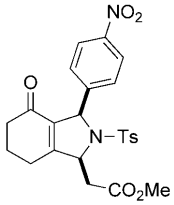


Methyl 2-[3-(Naphthalen-1-yl)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3f)



Obtained in 83% yield (101 mg) after purification with a heptane/ethyl acetate gradient ($R_f=0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta=8.22$ (d, $J=8.6$ Hz, 1H), 7.66 (d, $J=8.6$ Hz, 1H), 7.57 (d, $J=7.5$ Hz, 1H), 7.46 (ddd, $J=8.6$, 6.9 and 1.6 Hz, 1H), 7.4–7.3 (m, 3H), 7.2–7.1 (m, 2H), 6.85 (d, $J=8.6$ Hz, 2H), 6.36 (br, m, 1H, N-CHAr), 5.20 (br, m, 1H NCH), 3.71 (s, 3H, OMe), 3.23 (dd, $J=15.9$ and 3.8 Hz, 1H, CH_2CO_2Me), 3.06 (dd, $J=15.9$ and 7.9 Hz, 1H, CH_2CO_2Me), 2.4–2.2 (m, 4H), 2.15 (s, 3H Me), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=194.2$ (CO), 171.1 (CO_2Me), 157.5 (*C*=C-CO), 143.7 (C), 136.5 (C), 136.2 (C), 134.4 (C), 133.6 (C), 131.4 (C), 129.2, 128.5, 128.3, 128.0, 126.0, 125.6, 125.0, 123.4, 65.4 (NCHAr), 63.2 (NCH), 52.2 (OMe), 40.1 (CH_2CO_2Me), 37.8 (CH_2CO), 23.8, 23.1, 21.5 (Me); HR-MS (ESI): $m/z=512.1500$, calcd. for $C_{28}H_{27}NO_5S$ $[M+Na]^+$: 512.1508; IR (neat): $\nu=1734$, 1677 cm^{-1}.

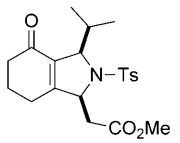
Methyl 2-[3-(4-Nitrophenyl)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3g)



Obtained in 47% yield (57 mg) after purification with a heptane/ethyl acetate gradient ($R_f=0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta=8.04$ (d, $J=8.8$ Hz, 2H), 7.59 (d, $J=7.6$ Hz, 2H), 7.46 (d, $J=8.8$ Hz, 2H), 7.21 (d, $J=7.6$ Hz, 2H), 5.59 (d, $J=2.4$ Hz, 1H, N-CHAr), 4.96 (br, m, 1H NCH), 3.72 (s, 3H, OMe), 2.96 (dd, $J=16.1$ and 3.9 Hz, 1H, CH_2CO_2Me), 3.15 (dd, $J=16.1$ and 7.3 Hz, 1H, CH_2CO_2Me), 2.38 (s, 3H Me), 2.3–2.2 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=194.3$(CO), 170.7 (CO_2Me),

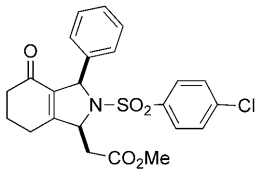
159.7 (*C*=C-CO), 147.3 (C), 144.8 (C), 134.3 (C), 133.8 (C), 130.2 (C), 128.9, 128.1, 123.6, 67.7 (NCHAr), 65.9 (NCH), 52.4 (OMe), 39.8 (CH_2CO_2Me), 37.7 (CH_2CO), 23.8, 22.9, 21.7 (Me); HR-MS (ESI): m/z = 507.1187, calcd. for $C_{24}H_{24}N_2O_7S$ $[M+Na]^+$: 507.1202; IR (neat): ν = 1733, 1676 cm^{-1}.

Methyl 2-(3-Isopropyl-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)acetate (3h)



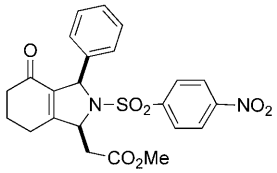
Obtained in 71% yield (72 mg) after purification with a heptane/ethyl acetate gradient (R_f = 0.3 in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.67 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 4.76 (ddd, J = 8.9, 4.0 and 1.2 Hz, 1H, NCH), 4.57 (d, J = 2.2 Hz, 1H, N-CHAr), 3.72 (s, 3H, OMe), 3.04 (dd, J = 16.3 and 4.2 Hz, 1H, CH_2CO_2Me), 2.66 (dd, J = 16.3 and 8.8 Hz, 1H, CH_2CO_2Me), 2.38 (s, 3H Me), 2.3–2.2 (m, 1H), 2.1–2.2 (m, 1H), 1.9–1.8 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H, Me) 0.97 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$): δ = 195.2 (CO), 171.2 (CO_2Me), 159.2 (*C*=C-CO), 144.1 (C), 135.2 (C), 133.8 (C),130.0, 128.0, 71.1 (NCHAr), 65.9 (NCH), 52.3 (OMe), 40.6 (CH_2CO_2Me), 37.9 (CH_2CO), 32.8, 23.1, 21.7, 19.7, 18.8 (Me); HR-MS (ESI): m/z = 428.1501, calcd. for $C_{21}H_{27}NO_5S$ $[M+Na]^+$: 428.1508; IR (neat): ν = 1735, 1672 cm^{-1}.

Methyl 2-[2-(4-Chlorophenylsulfonyl)-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3i)



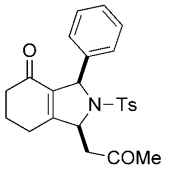
Obtained in 82% yield (94 mg) after purification with a heptane/ethyl acetate gradient (R_f = 0.3 in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.50 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.5–7.1 (m, 5H), 5.51 (d, J = 2.1 Hz, 1H, N-CHAr), 4.93 (br, m, 1H NCH), 3.58 (s, 3H, OMe), 2.98 (dd, J = 15.9 and 4.0 Hz, 1H, CH_2CO_2Me), 2.81 (dd, J = 15.9 and 7.5 Hz, 1H, CH_2CO_2Me), 2.2–2.1 (m, 4H), 1.9–1.7 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 194.3 (CO), 170.6 (CO_2Me), 158.2 (*C*=C-CO), 139.5 (C), 139.4, 136.5 (C), 135.1 (C), 129.4, 129.2, 128.4, 128.1, 127.8, 127.2, 68.5 (NCHAr), 65.7 (NCH), 52.2 (OMe), 40.0 (CH_2CO_2Me), 37.8 (CH_2CO), 23.7, 23.0; HR-MS (ESI): m/z = 482.0794, calcd. for $C_{23}H_{22}ClNO_5S$ $[M+Na]^+$: 482.0805; IR (neat): ν = 1732, 1674 cm^{-1}.

Methyl 2-[2-(4-nitrophenylsulfonyl)-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl]acetate (3j)



Obtained in 44% yield (52 mg) after purification with a heptane/ethyl acetate gradient (R_f = 0.3 in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ = 8.15 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.19 (br, m, 5H), 5.69 (d, J = 2.4 Hz, 1H, N-CHPh), 5.13 (br, m, 1H NCH), 3.66 (s, 3H, OMe), 3.06 (dd, J = 15.8 and 4.4 Hz, 1H, CH_2CO_2Me), 2.94 (dd, J = 15.8 and 7.1 Hz, 1H, CH_2CO_2Me), 2.5–2.2 (m, 4H), 2.1–2.0 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 194.1 (CO), 170.4 (CO_2Me), 157.7 (*C*=C-CO), 150.2 (C), 144.4 (C), 139.0 (C), 135.0 (C), 129.0, 128.6, 128.5, 127.9, 124.2, 68.8 (NCHAr), 65.9 (NCH), 52.4 (OMe), 39.6 (CH_2CO_2Me), 37.9 (CH_2CO), 23.8, 23.1; HR-MS (ESI): m/z = 493.1064, calcd. for $C_{23}H_{22}N_2O_7S$ $[M+Na]^+$: 493.1045; IR (neat): ν = 1732, 1675 cm^{-1}.

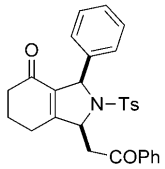
1-(2-Oxopropyl)-3-phenyl-2-tosyl-2,3,6,7-hexahydro-1*H*-isoindol-4(5*H*)-one (6a)



Obtained in 91% yield (96 mg) after purification with a heptane/ethyl acetate gradient (R_f = 0.3 in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.61 (d, J = 8.3 Hz, 2H), 7.29–7.16 (m, 7H), 5.61 (d, J = 1.2, 1H, N-CHAr), 5.03 (ddd, J = 7.9, 4.0 and 1.2 Hz, 1H, NCH), 3.22 (dd, J = 17.4 and 3.3 Hz, 1H, CH_2COMe), 2.93 (dd, J = 17.4 and 7.9 Hz, 1H, CH_2COMe), 2.34 (s, 3H, Me), 2.2–2.0 (m, 4H), 2.13 (s, 3H, COMe), 1.9–1.7 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 205.7 (COMe), 194.3 (CO), 159.2 (*C*=C-CO), 144.1 (C), 140.3 (C), 134.8 (C), 134.0 (C), 130.0 (C), 128.3, 127.9, 129.8, 127.7, 68.1 (NCHAr), 64.4 (NCH), 49.2 (CH_2COMe), 37.7 (CH_2CO), 30.9 (*C*OMe) 23.7, 22.9, 21.6 (Me); HR-MS (ESI): m/z = 446.1416, calcd. for $C_{24}H_{25}NO_4S$ $[M+Na]^+$: 446.1402; IR (neat): ν = 1711, 1671 cm^{-1}.

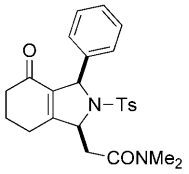
1-(2-Oxo-2-phenylethyl)-3-phenyl-2-tosyl-2,3,6,7-hexahydro-1*H*-isoindol-4(5*H*)-one (6b)

Obtained in 47% yield (57 mg) after purification with a heptane/ethyl acetate gradient (R_f = 0.3 in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.9–7.8 (m, 1H), 7.7–7.6 (m, 1H), 7.6–7.5 (m, 2H), 7.5–7.4 (m, 1H), 7.4–7.3 (m, 2H), 7.3–7.1 (m, 7H), 5.47 (d, J = 1.7, 1H, N-CHAr), 5.17 (ddd, J = 8.9, 3.0 and 1.7 Hz, 1H, NCH), 3.76 (dd, J = 17.4 and 3.1 Hz, 1H, CH_2CO_2Ar), 3.44 (dd, J = 17.4 and 8.9 Hz, 1H, CH_2CO_2Ar), 2.29 (s, 3H, Me), 2.2–2.1 (m, 4H), 2.0–1.8 (m,



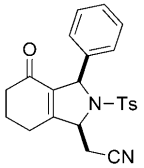
2H); ^{13}C NMR ($CDCl_3$): $\delta = 197.4$ (COAr), 194.6 (CO), 159.8 (*C*=C-CO), 144.2 (C), 140.4 (C), 134.0 (C), 130.1 (C), 130.0 (C), 129.0, 128.5, 128.0, 127.7, 126.6, 68.2 (NCHAr), 65.2 (N*C*H), 45.3 (CH_2COAr), 37.9 (CH_2CO), 24.2, 23.1, 21.7 (Me); HR-MS (ESI): $m/z = 508.1582$, calcd. for $C_{29}H_{27}NO_4S$ $[M+Na]^+$: 508.1559; IR (neat): $\nu = 1671$ cm^{-1}.

N,N-Dimethyl-2-(4-oxo-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)acetamide (6c)



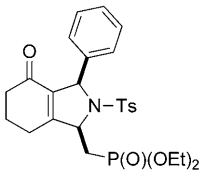
Obtained in 68% yield (77 mg) after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.68$ (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.3–7.1 (m, 5H), 6.86 (d, $J = 8.0$ Hz, 1H), 5.44 (br, m, 1H, N-CHAr), 4.90 (br, m, 1H, NCH), 3.0–2.9 (m, 2H, CH_2CONMe_2), 2.90 (s, 3H, NMe_2), 2.84 (s, 3H, NMe_2), 2.35 (s, 3H, Me), 2.2–1.8 (m, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 194.7$ (CO), 169.5 (CH_2CONMe_2), 160.7 (*C*=C-CO), 144.3 (C), 140.4 (C), 134.4 (C), 133.7 (C), 130.1 (C), 128.3, 128.0, 127.9, 68.1 (NCHAr), 66.9 (N*C*H), 39.1 (CH_2CONMe_2), 37.8 (NMe_2), 35.7 (NMe_2), 24.3, 23.1, 21.7 (Me); HR-MS (ESI): $m/z = 475.1662$, calcd. for $C_{25}H_{28}N_2O_4S$ $[M+Na]^+$: 475.1668; IR (neat): $\nu = 1674$, 1643 cm^{-1}.

2-(4-Oxo-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)acetonitrile (6d)



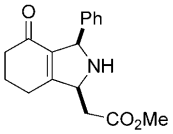
Obtained in 32% yield (32 mg) after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.44$ (d, $J = 8.3$ Hz, 2H), 7.3–7.2 (m, 2H), 7.1–7.0 (m, 5H), 5.46 (d, $J = 2.3$ Hz, 1H, N-CHAr), 4.73 (br, m, 1H, NCH), 3.0–2.9 (m, 2H, CH_2CN), 2.26 (s, 3H, Me), 2.2–2.1 (m, 4H), 2.0–1.9 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 194.0$ (CO), 154.9 (*C*=C-CO), 144.6 (C), 138.8 (C), 136.7 (C), 134.3 (C), 130.0 (C), 128.4, 128.2, 128.1, 127.9, 116.7 (CN), 68.7 (NCHAr), 64.6 (N*C*H), 37.9 (CH_2CN), 23.9, 23.1, 21.7 (Me); HR-MS (ESI): $m/z = 429.1258$, calcd. for $C_{23}H_{22}N_2O_3S$ $[M+Na]^+$: 429.1249; IR (neat): $\nu = 1676$, 2220 cm^{-1}.

Diethyl (4-Oxo-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)methylphosphonate (6e)



Obtained in 41% yield (53 mg) after purification with a heptane/ethyl acetate gradient ($R_f = 0.3$ in cyclohexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): $\delta = 7.57$ (d, $J = 8.4$ Hz, 2H), 7.2–7.1 (m, 7H), 5.44 (br, m, 1H, N-CHAr), 4.76 (br, m, 1H, NCH), 4.1–3.9 (m, 4H, OCH_2), 2.7–2.5 (m, 2H, $CH_2PO(OEt)_2$), 2.29 (s, 3H, Me), 2.2–2.0 (m, 4H), 1.3–1.2 (m, 6H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 194.7 (CO), 159.5 (*C*=C-CO), 144.2 (C), 140.0 (C), 135.3 (C), 134.3 (C), 130.1 (C), 128.4, 128.0, 127.9, 127.7, 68.0 (NCHAr), 64.3 (N*C*H), 62.3 (d, $J = 6.6$ Hz, OCH_2), 62.0 (d, $J = 6.6$ Hz, OCH_2), 37.8, 34.2, 32.4 ($CH_2PO(OEt)_2$), 29.8, 24.1, 23.2, 16.4 (d, $J = 6.0$ Hz, Me), 16.3 (d, $J = 6.0$ Hz, Me); ^{31}P NMR ($CDCl_3$): $\delta = 25.5$; HR-MS (ESI): $m/z = 540.1597$, calcd. for $C_{26}H_{32}NO_6PS$ $[M+Na]^+$: 540.1586; IR (neat): $\nu = 1676$ cm^{-1}.

N-Deprotection Procedure: Synthesis of Methyl (1*S**,3*R**)-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl)-acetate (3j′)



To a solution of methyl {(1*S**,3*R**)-2-[(4-nitrophenyl)sulfonyl]-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-yl}acetate **3j** (30 mg, 0.06 mmol) and K_2CO_3 (35 mg, 0.25 mmol, 4.0 equiv.) in CH_3CN-DMSO (95:5) (1 mL) at room temperature was added PhSH (23 μL, 0.22 mmol). The reaction mixture was heated at 40 °C for 2 h. The crude mixture was diluted with AcOEt (10 mL) and 1N HCl (10 mL) and the layers were separated. The aqueous layer was basified with solid K_2CO_3 (pH 10–11) and extracted with AcOEt (3× 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide **3j′**; yield: 12 mg (66%). ^{1}H NMR ($CDCl_3$): $\delta = 7.34$ (d, $J = 7.1$ Hz, 2H), 7.30 (dd, $J = 7.1$ and 6.9 Hz, 2H),7.22 (t, $J = 6.9$ Hz, 1H), 5.25 (s, 1H, N-CHPh), 4.59 (dd, $J = 4.4$ and 4.1 Hz, 1H, NCH), 3.71 (s, 3H, OMe), 2.79 (dd, $J = 15.6$ and 4.1 Hz, 1H, CH_2CO_2Me), 2.60 (dd, $J = 15.6$ and 4.4 Hz, 1H, CH_2CO_2Me), 2.51–2.30 (m, 4H), 2.22 (br, s, NH), 1.55–1.26 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 195.6$ (CO), 171.8 (CO_2Me), 162.3 (*C*=C-CO), 143.6 (C), 138.2 (C), 128.2, 127.5, 127.2, 65.7 (NCHPh), 63.1 (NCH), 51.9 (OMe), 41.0 (CH_2CO_2Me), 38.2 (CH_2CO), 23.8, 23.5; HR-MS (ESI): $m/z = 286.1449$, calcd. for $C_{17}H_{19}NO_3$ $[M+H]^+$: 286.1443; IR (neat): $\nu = 1733$, 1669 cm^{-1}.

Computational Methods

Geometry optimization was carried out at the B97-D level of theory[17] with the def2-TZVPP basis set.[18] These calculations were accelerated using the Multipole Accelerated Resolution of Identity for J (MARI-J) approximation method,[19] as implemented in Turbomole 6.2.[20] LUMO have been drawn using the gOpenMol 3.00 package.[21] The molecular orbital coefficients have been computed at the HF/STO-3G level, based on the DFT gas-phase geometries.[16c] Hückel calculations were carrried out with the Hückel simple program.[22]

Acknowledgements

We are grateful to ICSN and to the Agence Nationale de la Recherche (ANR) for financial support. This work has been done within the PhoSciNet COST action.

References

[1] For recent representative examples, see: a) T. J. Watson, T. A. Ayers, N. Shah, D. Wenstrup, M. Webster, D. Freund, S. Horgan, J. P. Carey, *Org. Process Res. Dev.* **2003**, *7*, 521–532; b) P.-P. Kung, B. Huang, G. Zhang, J. Z. Zhou, J. Wang, J. A. Digits, J. Skaptason, S. Yamazaki, D. Neul, M. Zientek, J. Elleraas, P. Mehta, M.-J. Yin, M. J. Hickey, K. S. Gajiwala, C. Rodgers, J. F. Davies II, M. R. Gehring, *J. Med. Chem.* **2010**, *53*, 499–503; c) S. Van Goethem, P. Van der Veken, V. Dubois, A. Soroka, A.-M. Lambeir, X. Chen, A. Haemers, S. Scharpé, I. De Meester, K. Augustyns, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4159–4162.

[2] a) D. Achard, S. Grisoni, E. James-Surcouf, J.-L. Malleron, A. Morgat, J.-F. Peyronel, J.-F. Sabuco, M. Tabart, (Rhône–Poulenc Rorer S.A.), Patent WO 95/04040, **1995**; b) J.-D. Bourzat, A. Commerçon, N. Dereu, P. Mailliet, F. Sounigo-Thompson, J.-P. Martin, M. Capet, M. Cheve, (Rhône Poulenc-Rorer S.A.), Patent WO98/29390, **1998**; c) P. Mailliet, C. Salagnad, (Aventis Pharma S.A.), Patent WO01/07408, **2001**; d) F. Gasparini, Y. Auberson, S. Ofner, (Novartis Pharma GMBH), Patent WO03/047581, **2003**; e) V. J. Santora, J. A. Covel, R. Hayashi, R. R. Webb, A. S. Ren, W. G. Chen, J. J. Duffield, J. B. Ibarra, M. Pulley, G. Semple, M. I. Weinhouse, (Arena Pharmaceuticals), Patent WO 2007/061741, **2007**; f) M. Ogata, H. Matsumoto, S. Shimizu, S. Kida, H. Nakai, K. Motokawa, H. Miwa, S. Matsuura, T. Yoshida, *Eur. J. Med. Chem.* **1991**, *26*, 889–906.

[3] a) K. Popandova-Yambolieva, C. Ivanov, *Synth. Commun.* **1986**, *16*, 57–61; b) J.-L. Malleron, J.-F. Peyronel, P. Desmazeau, C. M′Houmadi, C. Planiol, *Tetrahedron Lett.* **1995**, *36*, 543–546; c) D. Bonnet-Delpon, J.-P. Bégué, T. Lequeux, M. Ourevitch, *Tetrahedron* **1996**, *52*, 59–70.

[4] a) S. Mutti, C. Daubié, J. Malpart, X. Radisson, *Tetrahedron Lett.* **1996**, *37*, 8743–8746; b) H. Okamura, H. Shimizu, Y. Nakamura, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* **2000**, *41*, 4147–4150.

[5] For other methods, see: a) M. Westling, T. Livinghouse, *J. Am. Chem. Soc.* **1987**, *109*, 590–592; b) K. N. Clary, M. Parvez, T. G. Back, *J. Org. Chem.* **2010**, *75*, 3751–3760.

[6] For recent reviews on phosphine promoted annulation reactions, see: a) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; c) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140–1152; d) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102–3116; e) C. Nájera, J. M. Sansano, M. Yus, *J. Braz. Chem. Soc.* **2010**, *21*, 377–412; f) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174–194.

[7] M. Schuler, D. Duvvuru, P. Retailleau, J.-F. Betzer, A. Marinetti, *Org. Lett.* **2009**, *11*, 4406–4409.

[8] For other synthetic approaches to pyrrolines by phosphine organocatalysis, see: a) Z. Xu, X. Lu, *Tetrahedron Lett.* **1997**, *38*, 3461–3464; b) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031–5041; c) M. Shi, Y.-M. Xu, *Eur. J. Org. Chem.* **2002**, 696–701; d) X.-F. Zhu, C. E. Henry, O. Kwon, *Tetrahedron* **2005**, *61*, 6276–6282; e) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845; f) B. Zhang, Z. He, S. Xu, G. Wu, Z. He, *Tetrahedron* **2008**, *64*, 9471–9479; g) N. Fleury-Brégeot, L. Jean, P. Retailleau, A. Marinetti, *Tetrahedron* **2007**, *63*, 11920–11927; h) Y.-Q. Fang and E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661; i) N. Pinto, N. Fleury-Brégeot, A. Marinetti, *Eur. J. Org. Chem.* **2009**, 146–151.

[9] X. Fu, S. Zhang, J. Yin, T. L. McAllister, S. A. Jiang, C.-H. Tann, T. K. Thiruvengadam, F. Zhang, *Tetrahedron Lett.* **2002**, *43*, 573–576.

[10] CCDC 786106 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223–336033; e-mail: deposit@ccdc.cam.uk).

[11] Portionwise addition of the phosphine, that is, 15–20 mol% at the beginning of the reaction and again after 8 h heating, can be applied to increase conversion rates.

[12] E. Piers, J. R. Grierson, C. K. Lau, I. Nagakura, *Can. J. Chem.* **1982**, *60*, 210–223.

[13] A. B. Pulipaka, S. C. Bergmeier, *J. Org. Chem.* **2008**, *73*, 1462–1467.

[14] a) Y.-L. Shi, Y.-M. Xu, M. Shi, *Adv. Synth. Catal.* **2004**, *346*, 1220–1230; b) Y.-L. Shi, M. Shi, *Tetrahedron* **2006**, *62*, 461–475; c) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1–48.

[15] Only β-unsubstituted cyclic enones are common substrates for aza-Morita–Baylis–Hillman reactions: M. Shi, Y.-M. Xu, *Chem. Commun.* **2001**, 1876–1877.

[16] a) Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471; b) E. Mercier, B. Fonovic, C. Henry, O. Kwon, T. Dudding, *Tetrahedron Lett.* **2007**, *48*, 3617–3620; c) Y. Liang, S. Liu, Y. Xia, Y. Li, Z.-X. Yu, *Chem. Eur. J.* **2008**, *14*, 4361–4373.

[17] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787–1799.

[18] F. Weigend, M. Häser, H. Patzelt, R. Ahlrichs, *Chem. Phys. Lett.* **1998**, *294*, 143–152.
[19] M. Sierka, A. Hogekamp, R. Ahlrichs, *J. Chem. Phys.* **2003**, *118*, 9136–9148.
[20] R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165–169.
[21] a) L. Laaksonen, *J. Mol. Graph.* **1992**, *10*, 33–34; b) D. L. Bergman, L. Laaksonen, A. Laaksonen, *J. Mol. Graph. Model.* **1997**, *15*, 301–306.
[22] Hückel simple version 4.0. Jean-Yves Magna, **1998**. http://www.jymagna.com.

