A New Approach to Di- and Tetrasubstituted 2,3-Dihydropyridin-4(1*H*)-ones through Aza-Diels–Alder Reaction Promoted by Silicon Tetrachloride

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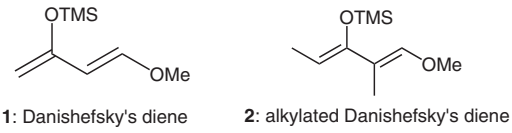
Abstract: Silicon tetrachloride promotes an aza-Diels–Alder reaction with a range of imines and Danishefsky's diene or an alkylated derivative, giving the desired products in good to excellent yields.

Key words: aza-Diels–Alder reaction, heterocycles, silicon tetrachloride

The aza-Diels–Alder reaction is a powerful method for the construction of six-membered nitrogen heterocycles.[1,2] Recent advances have been made in a number of Lewis acid catalyzed aza-Diels–Alder reactions in organic solvents,[3] aqueous media,[4] and ionic liquids.[5] Moreover, the use of Brønsted acid[6] and hydrogen-bond catalysis[7] provides an alternative to the use of metal catalysts. Asymmetric versions of this transformation have also been reported with several chiral metal complexes[8,9] or chiral Brønsted acid catalysts.[6]

Many examples of aza-Diels–Alder reactions in the presence of simple Danishefsky's diene **1** (Figure 1) have been reported, but surprisingly less attention has been paid to the reactivity of alkylated **2** and, to the best of our knowledge, the only diastereoselective versions reported in the literature concern the use of chiral or activated aldimines[10] and/or the use of alkylated dienes different from **2**.[9f,11]



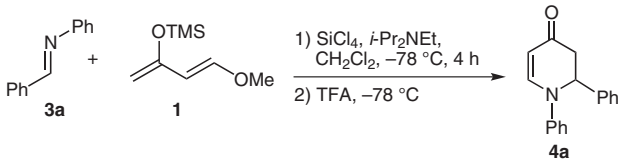
1: Danishefsky's diene **2**: alkylated Danishefsky's diene

Figure 1

Very recently the activation of the mild Lewis acid silicon tetrachloride with strong neutral Lewis bases, was introduced by Denmark in a number of very important carbon–carbon bond-forming reactions like aldol-type reactions.[12]

Now we report a new application of silicon tetrachloride in a versatile and efficient aza-Diels–Alder reaction of a range of imines with the Danishefsky dienes **1** and **2**. Moreover, the study of the reactivity of alkylated Danishefsky diene, **2**, allowed an easy approach to new tetrasubstituted 2,3-dihydropyridin-4(1*H*)-ones.

We first investigated the reaction of the representative imine **3a** with diene **1** in the presence of silicon tetrachloride according to Scheme 1. In the absence of silicon tetrachloride, the desired product was not detected and we recovered the unreacted imine **3a** (Table 1, entry 1), while the use of silicon tetrachloride gave the cyclic product **4a** in 72% yield in reasonable time (entry 2). The activation of silicon tetrachloride with a Lewis base like methyl *p*-tolyl sulfoxide (entry 3) was not necessary, giving almost unchanged yield. Interestingly, we observed also in our previous work on vinylogous aldol reactions a not negligible reactivity of Danishefsky's diene and masked forms of acetoacetate esters in the presence of nonactivated silicon tetrachloride.[13,14] At the end of the process, the use of trifluoroacetic acid was necessary to obtain the final adduct in high yield. In the absence of the acidic treatment, neutral aqueous workup afforded a complex mixture of products, which tended to decompose in the course of chromatography. The failure to isolate any intermediate did not allow to ascertain the mechanism for the formation of the dihydropyridinones through a [4+2] cycloaddition or a Mukaiyama vinylogous imino-aldol reaction.[2c]



Scheme 1

With these results in hand we further examined the possibility of developing a one-pot process with the combination of the synthesis of imine, in the presence of activated molecular sieves, and the following aza-Diels–Alder reaction (Table 2, entry 1, Scheme 2).

In this way the adduct **4a** was obtained in comparable yield and in shorter reaction time (1 h), while longer reaction time gave almost quantitative yield (entry 2). Several imines were reacted according to the modified one-pot procedure.

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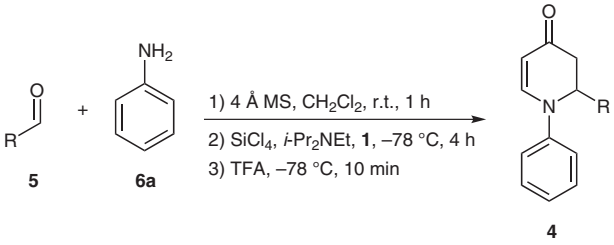
Table 1 Aza-Diels–Alder Reaction of **3a** with Danishefsky's Diene (**1**)

Entry	$MeS(O)(4\text{-}MeC_6H_4)$ (equiv)	$SiCl_4$ (equiv)	Yield (%)[a,b]
1	–	–	–
2	–	1	72
3	0.1	1	73

[a] All the yields refer to isolated chromatographically pure compounds.
[b] The product was characterized by comparison of spectroscopic data with those reported in literature.



Scheme 2

The reported data show a very good reactivity for several aromatic and heteroaromatic imines, while imines derived from unsaturated or aliphatic aldehydes did not react (Table 2, entries 7 and 8) even after the activation of silicon tetrachloride by methyl *p*-tolyl sulfoxide. A different behavior was shown by imines both with the strong electron-withdrawing nitro group and with electron-releasing groups on the aromatic ring (entries 9–13). The presence of a nitro group on the aldehyde aromatic moiety of the imine decreased the reactivity (entry 9) and the activation of silicon tetrachloride was required to obtain higher yield (entry 10). The lower reactivity of aldimines **5i**, **5j**, and **5k** and their order of reactivity, respectively 4-Me > 4-F > 4-MeO, can reasonably be attributed to the effect of the electron-releasing groups that decrease the electrophilicity of carbonyl compounds and imines (entries 11–13).

The problem of the low reactivity of 4-MeO derivatives of **5k** (Table 3, entries 1 and 2) was resolved using an imine activated by a strong electron-withdrawing group on the aromatic ring of parent amine. In fact, the corresponding pyridinone **4kc** could be isolated in good yield by performing the reaction at –50 °C on the imine derived from 4-nitroaniline **6c** and in the presence of the methyl *p*-tolyl sulfoxide for the activation of silicon tetrachloride (Table 3, entry 5, Scheme 3).

Table 2 Aza-Diels–Alder Reaction with Danishefsky's Diene (**1**)

Entry	Aldehyde, R			Yield (%)[a,b] of **4**
1[c]	**5a**	Ph	**4a**	73
2	**5a**	Ph	**4a**	95
3	**5b**	$4\text{-}ClC_6H_4$	**4b**	83
4	**5c**	2-furyl	**4c**	95
5	**5d**	2-pyridyl	**4d**	94
6	**5e**	$4\text{-}F_3CC_6H_4$	**4e**	77
7[d]	**5f**	PhCH=CH	**4f**	–
8[d]	**5g**	$PhCH_2CH_2$	**4g**	–
9	**5h**	$4\text{-}O_2NC_6H_4$	**4h**	26
10[d]	**5h**	$4\text{-}O_2NC_6H_4$	**4h**	93
11	**5i**	$4\text{-}MeC_6H_4$	**4i**	66
12	**5j**	$4\text{-}FC_6H_4$	**4j**	40
13	**5k**	$4\text{-}MeOC_6H_4$	**4k**	–

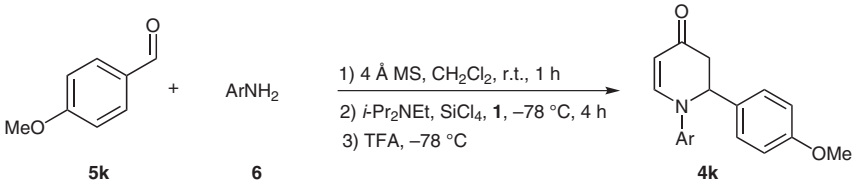
[a] All the yields refer to isolated chromatographically pure compounds.
[b] The products were characterized by comparison of spectroscopic data with those reported in literature.
[c] Reaction time = 1 h.
[d] The reactions were performed using 0.1 equiv of methyl *p*-tolyl sulfoxide.

Table 3 Aza-Diels Alder Reaction of 4-Methoxy Derivative **5k** with Danishefsky's Diene **1**

Entry	Amine, Ar		$MeS(O)(4\text{-}MeC_6H_4)$ (equiv)	Yield (%)[a] of **4**	
1	**6a**	Ph	–	**4ka**	–
2	**6a**	Ph	0.1	**4ka**	27
3	**6b**	$2\text{-}MeOC_6H_4$	–	**4kb**	32
4	**6c**	$4\text{-}O_2NC_6H_4$	–	**4kc**	47
5[b]	**6c**	$4\text{-}O_2NC_6H_4$	0.1	**4kc**	70

[a] All the yields refer to isolated chromatographically pure compounds.
[b] Reaction temperature = –50 °C.

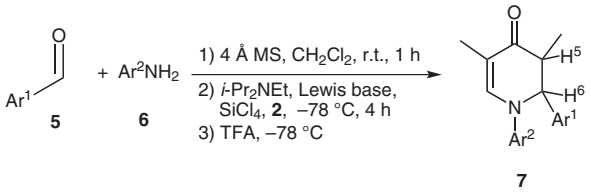
In the optimized reaction conditions of the one-pot procedure, the alkylated diene **2** was successfully used in the formation of a new cyclic tetrasubstituted adducts **7** (Table 4, Scheme 4). In preliminary experiments we



Scheme 3

noted a lower reactivity of **2** with respect to the simple diene **1**, (entries 1 and 2, Table 4). The cyclic adducts were obtained in satisfactory yield only when silicon tetrachloride was activated by methyl *p*-tolyl sulfoxide. The observed diastereoselectivity was found to be 66:34 in favor of the *trans* diastereomer. The two diastereomers were generally separated by chromatography. The *cis* relationship was assigned on the basis of a larger $J_{H\text{-}5,H\text{-}6}$ (Scheme 4), according to what was reported for the oxygenated analogous pyranones.[15] After these preliminary results, we examined the reactivity of several imines obtained by the combination of several amines and aldehydes. The presence of a 4-methoxy group on the aromatic ring bound to the nitrogen atom completely deactivated the imine (entry 3), even after Lewis base activation of silicon tetrachloride (entry 4). In the presence of a nitro group we obtained high yields (entries 5–7), but unfortunately, at the expense of the diastereoselectivity. Then, we turned the attention to the influence of different substituents on the aromatic ring of the aldehyde moiety of the imines. In these cases, we noted again a strong electronic effect on the reactivity.

Under the standard reaction conditions, electron-withdrawing groups gave higher yield (entries 8–10 and 13–17), while substituents like methyl and methoxy completely inhibited the reactivity (entries 11 and 12). Concerning the diastereoselectivity, substituents in the *para* position gave a slight excess of the *cis* product (entries 8–10). However, in the presence of substituents in the *ortho* position, the ratio was significantly inverted in favor of the *trans* diastereomer (entries 13–17). This effect was minimized in the presence of 2-cyano (entry 13), a group with a well-known coordination ability.[12a]



Scheme 4

Different Lewis bases like DMF and pyridine *N*-oxide were also effective in the activation of silicon tetrachloride and they gave the adduct **7j** in slightly higher yields and with a slight decrease of diastereoselectivity with respect to methyl *p*-tolyl sulfoxide (entries 16 and 17).

In summary, we have described here a new application of silicon tetrachloride in aza-Diels–Alder reaction of several imines with Danishefsky's dienes **1** and **2**. The cyclic

Table 4 Aza-Diels–Alder Reaction on Different Aldimines with Diene **2**

Entry	Ar^1 of aldehyde	Ar^2 of amine	Lewis base (0.1 equiv)	Yield (%)[a]		*cis*/*trans*[b]
1	Ph	Ph	–	**7a**	–	–
2	Ph	Ph	MeS(O)(4-MeC_6H_4)	**7a**	82	66:34
3	Ph	4-$MeOC_6H_4$	–	–	–	–
4	Ph	4-$MeOC_6H_4$	MeS(O)(4-MeC_6H_4)	–	–	–
5	Ph	4-$O_2NC_6H_4$	–	**7b**	86	55:45
6	4-Cl	4-$O_2NC_6H_4$	MeS(O)(4-MeC_6H_4)	**7c**	50	55:45
7[c]	4-Cl	4-$O_2NC_6H_4$	MeS(O)(4-MeC_6H_4)	**7c**	95	50:50
8	4-$O_2NC_6H_4$	Ph	MeS(O)(4-MeC_6H_4)	**7d**	96	68:32
9	4-NCC_6H_4	Ph	MeS(O)(4-MeC_6H_4)	**7e**	65	67:33
10	4-ClC_6H_4	Ph	MeS(O)(4-MeC_6H_4)	**7f**	73	68:32
11	4-MeC_6H_4	Ph	MeS(O)(4-MeC_6H_4)	**7g**	0	–
12	4-$MeOC_6H_4$	Ph	MeS(O)(4-MeC_6H_4)	**7h**	0	–
13	2-NCC_6H_4	Ph	MeS(O)(4-MeC_6H_4)	**7i**	90	42:58
14	2-ClC_6H_4	Ph	MeS(O)(4-MeC_6H_4)	**7j**	60	24:76
15	2-$O_2NC_6H_4$	Ph	MeS(O)(4-MeC_6H_4)	**7k**	73	20:80
16	2-ClC_6H_4	Ph	pyridine *N*-oxide	**7j**	73	27:73
17	2-ClC_6H_4	Ph	DMF	**7j**	70	27:73

[a] All the yields refer to isolated chromatographically pure compounds.
[b] The *cis*/*trans* diastereoisomeric ratios were determined by ^1H NMR analysis (400 MHz) on the crude products.
[c] Reaction temperature = –50 °C.

adducts were obtained in good to excellent yields. Particular attention was paid to the synthesis of novel tetrasubstituted 2,3-dihydropyridin-4(1*H*)-one using alkylated Danishefsky's diene **2**. In this case the observed diastereoselectivity was only moderate, but significantly dependent on the substitution pattern of the aldehyde moiety of the imine. Moreover an efficient one-pot procedure was developed with the combination of the synthesis of imine and the following aza-Diels–Alder reaction in the presence of activated molecular sieves.

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under dry N_2. All the solvents for the reactions were of reagent grade and were dried and distilled immediately before use (CH_2Cl_2 from CaH_2). Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The reagents (Aldrich and Fluka) were used without further purification. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. The NMR spectra were recorded on a Bruker DRX 400 spectrometer (400 MHz, ^{1}H; 100 MHz, ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Coupling constants *J* are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. IR spectra were recorded on a Bruker Vector 22 (frequencies 400–4000 cm^{-1}, resolution 2 cm^{-1}). Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

One-Pot Aza-Diels–Alder Reaction of Danishefsky's Diene 1 (or Diene 2); General Procedure

In a flame-dried, 2-necked, round-bottomed flask, aldehyde **5** (0.66 mmol) and aniline **6** (0.70 mmol) were added to activated 4 Å MS (0.7 g) in anhyd CH_2Cl_2 (2 mL) under argon. The reaction mixture was stirred at r.t. for 1 h. Then the mixture was diluted with anhyd CH_2Cl_2 (2 mL) and the temperature was lowered to –78 °C. At this temperature, activator (0.066 mmol, if required), *i*-Pr_2NEt (0.66 mmol), $SiCl_4$ (0.66 mmol, 1.0 M in CH_2Cl_2) and Danishefsky's diene **1** (or **2**, 0.71 mmol) were successively added. At the end of the reaction, the mixture was treated with a solution of trifluoroacetic acid (0.1 mL) in CH_2Cl_2 (1 mL). After about 15 min, the reaction was quenched with aq sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (50×3 mL), and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography with PE–EtOAc mixture (from 9:1 to 7:3) for adducts **4** and with PE–EtOAc mixture (from 95:5 to 8:2) to afford the pure cyclic adducts **7**.

The products **4a–k** are known compounds and were characterized by comparison of their spectroscopic data with those reported in the literature.[5,6]

***cis*-2,3-Dihydro-3,5-dimethyl-1,2-diphenylpyridin-4(1*H*)-one (*cis*-7a)**

The title compound was obtained as a yellow wax-like solid in 54% yield; R_f = 0.41 (PE–EtOAc, 7:3).

IR (KBr): 698, 756, 1188, 1258, 1305, 1498, 1593, 1621, 1651, 2863, 2938, 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.85 (s, 3 H, CH_3), 3.37 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 5.01 (d, *J* = 7.0 Hz, 1 H, CHC*H*), 6.99–7.05 (m, 4 H, ArH), 7.23–7.32 (m, 6 H, ArH), 7.52 (s, 1 H, C=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 12.8, 43.6, 67.6, 108.3, 118.1, 123.4, 127.7, 127.9, 128.6, 129.3, 136.3, 145.2, 145.6, 193.4.

ESI-MS: *m*/*z* = 278 (M + 1).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.47; H, 6.72; N, 5.23.

***trans*-2,3-Dihydro-3,5-dimethyl-1,2-diphenylpyridin-4(1*H*)-one (*trans*-7a)**

The title compound was obtained as a yellow wax-like solid in 28% yield; R_f = 0.35 (PE–EtOAc, 7:3).

IR (KBr): 697, 756, 1207, 1312, 1385, 1494, 1594, 1614, 2924 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 7.5 Hz, 3 H, CHC*H*$_3$), 1.77 (s, 3 H, CH_3), 2.78 (dq, *J* = 2.1, 7.5 Hz, 1 H, C*H*CH_3), 4.88 (br d, *J* = 2.1 Hz, 1 H, CHC*H*), 6.99–7.08 (m, 3 H, ArH), 7.24–7.32 (m, 7 H, ArH), 7.53 (s, 1 H, C=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 18.3, 47.6, 68.0, 108.2, 117.7, 123.5, 126.0, 127.5, 128.7, 129.4, 137.8, 144.0, 145.5, 194.5.

ESI-MS: *m*/*z* = 278 (M + 1).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.40; H, 6.79; N, 5.24.

***cis*-2,3-Dihydro-3,5-dimethyl-1-(4-nitrophenyl)-2-phenylpyridin-4(1*H*)-one (*cis*-7b)**

The title compound was obtained as a yellow wax-like solid in 47% yield; R_f = 0.44 (PE–EtOAc, 7:3).

IR (KBr): 693, 750, 843, 1111, 1202, 1318, 1500, 1587, 2924 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 1.89 (s, 3 H, CH_3), 3.43 (quint, *J* = 6.9 Hz, 1 H, C*H*CH_3), 5.10 (d, *J* = 6.8 Hz, 1 H, CHC*H*), 7.06 (d, *J* = 7.3 Hz, 2 H, ArH), 7.30 (m, 5 H, ArH), 7.63 (s, 1 H, C=CH), 8.13 (d, *J* = 7.3 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 12.9, 43.9, 67.5, 112.6, 115.7, 125.5, 127.4, 128.5, 129.0, 135.1, 141.9, 142.8, 149.5, 193.4.

ESI-MS: *m*/*z* = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.56; H, 5.45; N, 8.85.

***trans*-2,3-Dihydro-3,5-dimethyl-1-(4-nitrophenyl)-2-phenylpyridin-4(1*H*)-one (*trans*-7b)**

The title compound was obtained as a yellow solid in 39% yield; mp 147 °C; R_f = 0.35 (PE–EtOAc, 7:3).

IR (KBr): 700, 780, 849, 959, 1121, 1242, 1344, 1490, 1579, 2936, 2987 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.4 Hz, 3 H, CHC*H*$_3$), 1.80 (s, 3 H, CH_3), 2.88 (dq, *J* = 1.9, 7.4 Hz, 1 H, C*H*CH_3), 4.98 (br d, *J* = 1.9 Hz, 1 H, CHC*H*), 7.05 (d, *J* = 7.5 Hz, 2 H, ArH), 7.99 (d, *J* = 7.2 Hz, 2 H, ArH), 7.26–7.30 (m, 3 H, ArH), 7.58 (s, 1 H, C=CH), 8.17 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 18.2, 47.8, 67.7, 112.2, 116.0, 125.6, 125.7, 128.1, 129.1, 136.4, 140.6, 142.3, 150.0, 194.7.

ESI-MS: *m*/*z* = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.59; H, 5.50; N, 8.53.

***cis*-2-(4-Chlorophenyl)-2,3-dihydro-3,5-dimethyl-1-(4-nitrophenyl)pyridin-4(1*H*)-one (*cis*-7c)**

The title compound was obtained as a yellow solid in 48% yield; mp 196 °C; R_f = 0.40 (PE–EtOAc, 7:3).

IR (KBr): 790, 869, 979, 1132, 1248, 1350, 1470, 1559, 1600, 2940, 2999 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 1.87 (s, 3 H, CH_3), 3.41 (quint, *J* = 6.9 Hz, 1 H, C*H*CH_3), 5.09 (d,

J = 6.9 Hz, 1 H, CHC*H*), 7.03 (d, *J* = 9.1 Hz, 2 H, ArH), 7.26 (m, 4 H, ArH), 7.60 (s, 1 H, C=CH), 8.11 (d, *J* = 9.1 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 12.8, 43.7, 66.7, 112.7, 115.8, 125.5, 128.8, 129.1, 133.6, 134.4, 141.7, 142.1, 149.2, 193.0.

ESI-MS: *m*/*z* = 357 (M + 1).

Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.69; H, 4.80; N, 7.85. Found: C, 63.78; H, 4.65; N, 7.71.

trans-2-(4-Chlorophenyl)-2,3-dihydro-3,5-dimethyl-1-(4-nitrophenyl)pyridin-4(1*H*)-one (_trans_-7c)

The title compound was obtained as a yellow solid in 47% yield; mp 198 °C; R_f = 0.33 (PE–EtOAc, 7:3).

IR (KBr): 791, 866, 989, 1135, 1260, 1355, 1476, 1549, 1605, 2930, 3000 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.3 Hz, 3 H, CHCH_3), 1.81 (s, 3 H, CH_3), 2.86 (dq, *J* = 1.7, 7.2 Hz, 1 H, C*H*CH_3), 4.98 (br d, *J* = 1.7 Hz, 1 H, CHC*H*), 7.05 (d, *J* = 9.2 Hz, 2 H, ArH), 7.16 (d, *J* = 8.4 Hz, 2 H, ArH), 7.32 (d, *J* = 8.4 Hz, 2 H, ArH), 7.58 (s, 1 H, C=CH), 8.17 (d, *J* = 9.2 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 18.2, 47.7, 67.3, 112.5, 116.1, 125.8, 127.3, 129.5, 134.1, 135.2, 140.5, 142.6, 149.9, 194.4.

ESI-MS: *m*/*z* = 357 (M + 1).

Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.69; H, 4.80; N, 7.85. Found: C, 63.91; H, 4.62; N, 7.68.

cis-2,3-Dihydro-3,5-dimethyl-2-(4-nitrophenyl)-1-phenylpyridin-4(1*H*)-one (_cis_-7d)

The title compound was obtained as a yellow solid in 65% yield; mp 142 °C; R_f = 0.38 (PE–EtOAc, 7:3).

IR (KBr): 753, 790, 849, 1190, 1234, 1308, 1359, 1510, 1581, 2933 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.0 Hz, 3 H, CHCH_3), 1.83 (s, 3 H, CH_3), 3.39 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 5.16 (d, *J* = 7.0 Hz, 1 H, CHC*H*), 6.93 (d, *J* = 8.0, 2 H, ArH), 7.04 (t, *J* = 8.0 Hz, 1 H, ArH), 7.24 (t, *J* = 8.0 Hz, 2 H, ArH), 7.48 (d, *J* = 8.6 Hz, 2 H, ArH), 7.53 (s, 1 H, C=CH), 8.11 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 12.7, 40.7, 66.8, 108.7, 118.4, 123.7, 124.0, 128.7, 129.4, 143.8, 144.5, 145.5, 147.5, 192.5.

ESI-MS: *m*/*z* = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.92; H, 5.81; N, 8.55.

trans-2,3-Dihydro-3,5-dimethyl-2-(4-nitrophenyl)-1-phenylpyridin-4(1*H*)-one (_trans_-7d)

The title compound was obtained as a yellow wax-like solid in 31% yield; R_f = 0.23 (PE–EtOAc, 7:3).

IR (KBr): 700, 780, 849, 959, 1121, 1242, 1344, 1490, 1579, 2936, 2987 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 7.3 Hz, 3 H, CHCH_3), 1.77 (s, 3 H, CH_3), 2.76 (dq, *J* = 2.2, 7.3 Hz, 1 H, C*H*CH_3), 4.96 (br d, *J* = 2.2 Hz, 1 H, CHC*H*), 6.95 (d, *J* = 7.8 Hz, 2 H, ArH), 7.10 (t, *J* = 7.3 Hz, 1 H, ArH), 7.30 (t, *J* = 7.8 Hz, 2 H, ArH), 7.43 (d, *J* = 8.6 Hz, 2 H, ArH), 7.54 (s, 1 H, C=CH), 8.16 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 18.1, 47.2, 67.4, 108.8, 117.7, 123.7, 124.0, 127.2, 129.6, 143.4, 144.5, 145.5, 147.5, 193.6.

ESI-MS: *m*/*z* = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.64; H, 5.48; N, 8.85.

cis-2-(4-Cyanophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (_cis_-7e)

The title compound was obtained as a yellow solid in 44% yield; mp 142 °C; R_f = 0.35 (PE–EtOAc, 7:3).

IR (KBr): 689, 756, 991, 1138, 1285, 1365, 1478, 1539, 1622, 2215, 2870, 2966, 2989 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.0 Hz, 3 H, CHCH_3), 1.84 (s, 3 H, CH_3), 3.39 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 5.08 (d, *J* = 7.0 Hz, 1 H, CHC*H*), 6.93 (d, *J* = 7.8 Hz, 2 H, ArH), 7.06 (t, *J* = 7.4 Hz, 1 H, ArH), 7.24–7.28 (m, 2 H, ArH), 7.42 (d, *J* = 8.2 Hz, 2 H, ArH), 7.51 (s, 1 H, C=CH), 7.58 (d, *J* = 8.3 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 12.7, 43.2, 67.1, 108.7, 111.7, 118.3, 118.5, 123.9, 128.5, 129.4, 132.3, 141.6, 144.3, 145.3, 192.3.

ESI-MS: *m*/*z* = 303 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.56; H, 6.12; N, 9.09.

trans-2-(4-Cyanophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (_trans_-7e)

The title compound was obtained as a yellow solid in 21% yield; mp 149 °C; R_f = 0.29 (PE–EtOAc, 7:3).

IR (KBr): 655, 688, 790, 1144, 1251, 1300, 1377, 1485, 1533, 1600, 2198, 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.2 Hz, 3 H, CHCH_3), 1.76 (s, 3 H, CH_3), 2.74 (dq, *J* = 2.2, 7.2 Hz, 1 H, CHCH_3), 4.91 (br d, *J* = 2.2 Hz, 1 H, CHC*H*), 6.95 (d, *J* = 7.8 Hz, 2 H, ArH), 7.10 (t, *J* = 7.4 Hz, 1 H, ArH), 7.25–7.37 (m, *J* = 8.0 Hz, 4 H, ArH), 7.52 (s, 1 H, C=CH), 7.60 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 18.1, 47.2, 67.5, 108.7, 111.6, 117.6, 118.2, 124.0, 127.0, 129.6, 132.6, 143.6, 143.7, 145.3, 193.7.

ESI-MS: *m*/*z* = 303 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.29; H, 6.15; N, 9.49.

cis-2-(4-Chlorophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (_cis_-7f)

The title compound was obtained as a yellow wax-like solid in 50% yield; R_f = 0.54 (PE–EtOAc, 7:3).

IR (KBr): 655, 670, 756, 889, 1150, 1288, 1268, 1370, 1452, 1577, 1627, 2863, 2999 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.0 Hz, 3 H, CHCH_3), 1.83 (s, 3 H, CH_3), 3.35 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 5.00 (d, *J* = 7.3 Hz, 1 H, CHC*H*), 6.96–7.06 (m, 3 H, ArH), 7.24–7.27 (m, 6 H, ArH), 7.50 (s, 1 H, C=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 12.7, 43.4, 66.9, 108.4, 118.9, 123.7, 128.7, 129.1, 129.3, 133.8, 134.8, 144.9, 145.5, 193.0.

ESI-MS: *m*/*z* = 312 (M + 1).

Anal. Calcd for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.31; H, 5.68; N, 4.29;

trans-2-(4-Chlorophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (_trans_-7f)

The title compound was obtained as a yellow wax-like solid in 23% yield; R_f = 0.44 (PE–EtOAc, 7:3).

IR (KBr): 672, 758, 882, 1148, 1227, 1332, 1490, 1584, 1624, 2944, 2987 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.2 Hz, 3 H, CHCH_3), 1.76 (s, 3 H, CH_3), 2.72 (dq, *J* = 2.1, 7.2 Hz, 1 H, C*H*CH_3), 4.84 (br d, *J* = 2.1 Hz, 1 H, CHC*H*), 6.97 (d, *J* = 8.0 Hz, 2 H, ArH), 7.08 (t,

J = 7.3 Hz, 1 H, ArH), 7.17 (d, *J* = 8.0 Hz, 2 H, ArH), 7.25–7.32 (m, 4 H, ArH), 7.50 (s, 1 H, C=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 18.1, 47.5, 67.3, 108.4, 117.7, 123.7, 126.0, 127.5, 128.9, 133.2, 136.4, 143.8, 145.3, 194.2.

ESI-MS: *m*/*z* = 312 (M + 1).

Anal. Calcd for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.30; H, 5.65; N, 4.66.

***cis*-2-(2-Cyanophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (*cis*-7i)**

The title compound was obtained as a yellow wax-like solid in 38% yield; R_f = 0.42 (PE–EtOAc, 7:3).

IR (KBr): 698, 756, 1188, 1258, 1305, 1498, 1593, 1621, 1651, 2210, 2863, 2938, 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.87 (s, 3 H, CH_3), 3.48 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 5.63 (d, *J* = 7.5 Hz, 1 H, CHC*H*), 6.99–7.01 (m, 2 H, ArH), 7.08 (t, *J* = 7.4 Hz, 1 H, ArH), 7.27 (m, 2 H, ArH), 7.35 (m, 1 H, ArH), 7.47–7.49 (m, 2 H, ArH, C=CH), 7.60–7.80 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 12.8, 42.5, 64.2, 108.0, 112.3, 117.5, 118.0, 118.8, 124.2, 127.7, 128.6, 129.5, 132.9, 133.6, 141.4, 145.9, 192.5.

ESI-MS: *m*/*z* = 303 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.58; H, 6.21; N, 9.08.

***trans*-2-(2-Cyanophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (*trans*-7i)**

The title compound was obtained as a yellow wax-like solid in 52% yield; R_f = 0.33 (PE–EtOAc, 7:3).

IR (KBr): 688, 743, 1100, 1232, 1320, 1377, 1490, 1594, 1632, 2200, 2932, 2958 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$), 1.81 (s, 3 H, CH_3), 2.83 (dq, *J* = 2.5, 7.2 Hz, 1 H, C*H*CH_3), 5.23 (br d, *J* = 2.5 Hz, 1 H, CHC*H*), 6.94 (d, *J* = 7.9 Hz, 2 H, ArH), 7.09 (t, *J* = 7.3 Hz, 1 H, ArH), 7.31–7.26 (m, 2 H, ArH), 7.36–7.45 (m, 3 H, ArH), 7.48 (s, 1 H, C=CH), 7.50 (d, *J* = 7.3 Hz, 1 H, ArH).

^{13}C NMR (100 MHz $CDCl_3$): δ = 12.9, 18.5, 47.2, 66.5, 108.3, 110.7, 116.9, 118.2, 119.0, 124.3, 126.5, 128.4, 129.7, 133.1, 134.0, 142.7, 144.9, 193.7.

ESI-MS: *m*/*z* = 303 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.60; H, 6.19; N, 9.08.

***cis*-7j**

We were not able to separate the minor *cis* diastereomer from the *trans*. It was obtained as an inseparable mixture with the *trans* isomer in 35% total yield.

***trans*-2-(2-Chlorophenyl)-2,3-dihydro-3,5-dimethyl-1-phenylpyridin-4(1*H*)-one (*trans*-7j)**

The title compound was obtained as a yellow wax-like solid in 38% yield; R_f = 0.46 (PE–EtOAc, 7:3).

IR (KBr): 718, 862, 1148, 1232, 1256, 1312, 1380, 1480, 1544, 1634, 2930, 2977 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$), 1.82 (s, 3 H, CH_3), 2.80 (dq, *J* = 1.7, 7.2 Hz, 1 H, C*H*CH_3), 5.22 (br d, *J* = 1.7 Hz, 1 H, CHC*H*), 6.93 (d, *J* = 8.4 Hz, 2 H, ArH), 7.04 (t, *J* = 7.3 Hz, 1 H, ArH), 7.15–7.41 (m, 6 H, ArH), 7.43 (s, 1 H, C=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 18.6, 45.4, 65.2, 107.7, 117.4, 118.3, 123.6, 126.9, 127.0, 129.0, 129.5, 130.5, 135.2, 144.6, 145.7, 194.5.

ESI-MS: *m*/*z* = 312 (M + 1).

Anal. Calcd for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.31; H, 5.69; N, 4.69;

***cis*-2,3-Dihydro-3,5-dimethyl-2-(2-nitrophenyl)-1-phenylpyridin-4(1*H*)-one (*cis*-7k)**

The title compound was obtained as a yellow wax-like solid in 15% yield; R_f = 0.40 (PE–EtOAc, 7:3).

IR (KBr): 734, 788, 845, 1003, 1190, 1234, 1358, 1365, 1532, 1600, 2943, 2978 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.84 (s, 3 H, CH_3), 3.98 (quint, *J* = 7.0 Hz, 1 H, C*H*CH_3), 6.24 (d, *J* = 7.5 Hz, 1 H, CHC*H*), 7.04–7.08 (m, 3 H, ArH), 7.27 (t, *J* = 8.4 Hz, 2 H, ArH), 7.39–7.46 (m, 2 H, ArH), 7.55 (s, 1 H, C=CH), 7.73 (d, *J* = 7.8 Hz, 1 H, ArH), 7.81 (d, *J* = 8.0 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 12.8, 43.3, 59.6, 108.2, 118.8, 124.1, 124.7, 128.9, 129.4, 131.3, 133.2, 138.1, 144.4, 146.0, 149.2, 192.5.

ESI-MS: 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.64; H, 5.75; N, 8.50.

***trans*-2,3-Dihydro-3,5-dimethyl-2-(2-nitrophenyl)-1-phenylpyridin-4(1*H*)-one (*trans*-7k)**

The title compound was obtained as a yellow wax-like solid in 58% yield; R_f = 0.34 (PE–EtOAc, 7:3).

IR (KBr): 710, 782, 849, 1120, 1223, 1370, 1434, 1559, 1600, 2965, 2997 cm^{-1}.

^{1}H NMR (400 MHz $CDCl_3$): δ = 1.41 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$), 1.80 (s, 3 H, CH_3), 2.59 (dq, *J* = 1.1, 7.2 Hz, 1 H, C*H*CH_3), 5.81 (br d, *J* = 1.1 Hz, 1 H, CHC*H*), 6.95 (d, *J* = 7.8 Hz, 2 H, ArH), 7.07 (t, *J* = 7.3 Hz, 1 H, ArH), 7.29 (m, 2 H, ArH), 7.42–7.46 (m, 1 H, ArH), 7.52 (m, 2 H, ArH), 7.64 (s, 1 H, C=CH), 8.10 (d, *J* = 8.0 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 19.2, 46.9, 63.7, 108.9, 117.5, 123.9, 126.4, 127.7, 128.9, 129.6, 133.7, 134.0, 144.4, 144.9, 147.3, 194.3.

ESI-MS: *m*/*z* = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.93, H, 5.44; N, 8.51.

Note Added in Proof

This paper is published despite the effects of the Italian law 133/08. This law drastically reduces public funds to public Italian universities, which is particularly dangerous for scientific free research, and will prevent young researchers from getting a position, either temporary or tenured, in Italy. One of the authors (A.M.) is protesting against this law to obtain its cancellation.

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References

(1) (a) *Organic Synthesis Highlights*; Waldmann, H., Ed.; VCH: Weinheim, **1995**, 2nd ed., 37. (b) Weinreb, S. M. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon: Oxford, **1991**, Chap. 2. (c) Weinreb, S. M. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon: Oxford, **1991**, Chap. 9. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon: Oxford, **1991**, 401. (e) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, **1987**.

(2) For reviews: (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, **1991**. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (c) Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558.

(3) (a) Jurcik, V.; Arai, K.; Salter, M. M.; YamashitaY, ; Kobayashi, S. *Adv. Synth. Catal.* **2008**, *350*, 647. (b) Patmore, N. J.; Hague, C.; Cotgreave, J. H.; Mahon, M. F.; Frost, C. G.; Weller, A. S. *Chem. Eur. J.* **2002**, *8*, 2088. (c) Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Lett.* **2001**, *42*, 7405. (d) Laurent-Robert, H.; Garrigues, B.; Dubac, J. *Synlett* **2000**, 1160. (e) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621. (f) Bari, L. D.; Guillarme, S.; Hermitage, S.; Howard, J. A. K.; Jay, D. A.; Pescitelli, G.; Whiting, A.; Yufit, D. S. *Synlett* **2004**, 708. (g) Hattori, K.; Yamamoto, H. *Synlett* **1993**, 129. (h) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (i) Morgan, P. E.; McCague, R.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 515. (j) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. With a solid catalyst: (k) Kumareswaran, R.; Reddy, B. G.; Vankar, Y. D. *Tetrahedron Lett.* **2001**, *42*, 7493. (l) Wang, Y.; Wilson, S. R. *Tetrahedron Lett.* **1997**, *38*, 4021.

(4) (a) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574. (b) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475. (c) Lock, R.; Waldmann, H. *Tetrahedron Lett.* **1996**, *37*, 2753.

(5) (a) Jurcik, V.; Wilhelm, R. *Org. Biomol. Chem.* **2005**, *3*, 239. (b) Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, *2*, 137.

(6) Aza-Diels–Alder reaction in MeOH without catalyst: Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309.

(7) Chiral Brønsted acid catalyzed aza-Diels–Alder reaction: Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796.

(8) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264.

(9) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 979. (b) Kobayashi, S.; Kusakabe, K.-i.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (c) Kobayashi, S.; Kusakabe, K.-i.; Komiyama, S.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225. (d) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (f) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3121. (g) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (h) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. (i) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (j) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (k) Mancheno, O. G.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. (l) Guillarme, S.; Whiting, A. *Synlett* **2004**, 711. (m) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905. (n) Bundu, A.; Guillarme, S.; Hannan, J.; Wan, H.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7849.

(10) (a) Andreassen, T.; Haland, T.; Hansen, L. K.; Gautun, O. R. *Tetrahedron Lett.* **2007**, *48*, 8413. (b) Rowland, G. B.; Rowland, E. B.; Zhang, O.; Antilla, J. C. *Curr. Org. Chem.* **2006**, *10*, 9. (c) Timmons, C.; Kattuboina, A.; McPherson, L.; Mills, J.; Li, G. *Tetrahedron* **2005**, *61*, 11837. (d) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (e) Badorrey, C.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1999**, *55*, 7601. (f) Yu, L.; Li, J.; Ramirez, J.; Chen, D.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903. (g) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594. (h) McFarlane, A. K.; Thomas, G.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2803. (i) Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983.

(11) (a) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587. (b) Ishimaru, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1997**, *53*, 5423.

(12) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199. (c) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

(13) Acocella, M. R.; De Rosa, M.; Massa, A.; Palombi, L.; Villano, R.; Scettri, A. *Tetrahedron* **2005**, *61*, 4091.

(14) Scettri, A.; Acocella, M. R.; Palombi, L.; Scalera, C.; Villano, R.; Massa, A. *Adv. Synth. Catal.* **2006**, *348*, 2229.

(15) Etayo, P.; Badorrey, R.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Eur. J. Org. Chem.* **2008**, 6008.