Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 11837–11842

Aza Diels–Alder reactions utilizing 4-iodo-2-trimethylsilyloxy-butadiene

Cody Timmons, Adiseshu Kattuboina, Lauren McPherson, James Mills and Guigen Li*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

Received 3 August 2005; revised 27 September 2005; accepted 10 October 2005

Available online 2 November 2005

Abstract—The aza Diels–Alder reaction is described for a novel diene. Imines bearing benzyl and aromatic protecting groups both work well. Moderate diastereoselectivities can be obtained using the simple α-methylbenzyl chiral auxiliary.

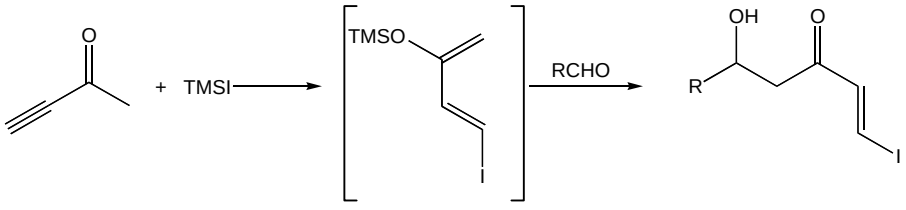
1. Introduction

The aza Diels–Alder reaction is among the most powerful methodologies for the construction of six-membered nitrogen heterocycles. Such compounds are of interest in the field of medicinal chemistry and have emerged as important building blocks in organic synthesis.[1]

Recently, a few reports have surfaced regarding the reaction of Danishefsky's diene and imines to produce dihydropyridones.[2] Such products are potentially quite versatile intermediates for the synthesis of *N*-heterocyclic natural products, such as indolizidines and related alkaloids.[3] Additionally, the enantioselective conjugate addition of nucleophiles to dihydropyridones has recently emerged as an important topic of interest in the field of asymmetric synthesis.[4]

As a whole, the majority of the Diels–Alder strategies for the preparation of dihydropyridones have utilized imines prepared from aniline or other similar aromatic amines. Such a strategy presents challenges with regard to the limited number of methods available for the removal of *N*-aryl protecting groups. A practically attractive alternative would be the use of more easily cleaved protecting group, such as tosyl[2f] or benzyl.

Recently, we have reported the preparation of a novel iodo diene from the reaction of 3-butyn-2-one and trimethylsilyl iodide (Scheme 1).[5] The diene has been characterized in situ by performing the reaction in deuterated solvent. This diene has been found to react with aldehydes in an aldol type fashion in either the absence or in the presence of an appropriate catalyst to produce the resulting halo-aldol type products in high yield and *E*/*Z* stereoselectivity. Such products contain several sites of functionalization and therefore are quite versatile synthetic intermediates. In an effort to extend the scope of this process, we sought to utilize imines as electrophilic acceptors to provide the analogous halo-Mannich type products. Such a reaction would complement our earlier methodology in which normal asymmetric halo-Mannich type products were obtained from the reaction between chiral cyclopropyl imides and imines in the presence of Et_2AlI and were cyclized to five-membered *N*-heterocycles.[6]



Scheme 1.

Keywords: Aza Diels–Alder; Dihydropyridones; Magnesium iodide.
* Corresponding author. Tel.: +1 806 742 3015; fax: +1 806 742 1289; e-mail: guigen.li@ttu.edu

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.018

2. Results and discussion

Initial attempts at this halo-Mannich reaction utilized the benzenesulfonyl-protected imine of 4-tolualdehyde. In the absence of catalyst, the desired product was formed in 20% yield after 24 h at 0 °C in CH_2Cl_2. The reaction was clean, with only starting materials and products observed in the crude reaction mixture. The structure of the product was confirmed by ^1H, ^{13}C, DEPT and 2-D NMR techniques (COSY and HMQC). In particular, a doublet at 5.56 ppm in the ^1H NMR spectrum was easily assigned as an N–*H* proton. In an effort to improve the yield, various conditions were explored. Extended reaction times did not lead to an increased conversion percentage. The use of other solvents (THF, ether, acetonitrile, toluene) failed to facilitate any improvements. When a number of Lewis acid catalysts ($TiCl_4$, $SnCl_4$, MgI_2, Et_2AlI) were screened, only the first two produced any product at all, while the use of the others all resulted in no product formation. Unfortunately, even with high catalyst loading (up to 100%) the highest yield obtained was ~35–40%. The use of 4-tosyl and 2-nosyl protecting groups were found to provide similar results.

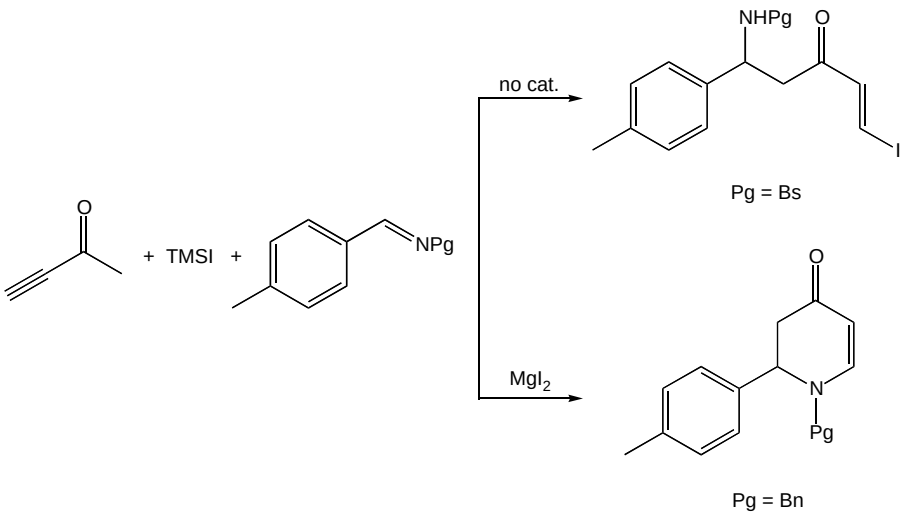
With these initial discouraging results in hand, we then turned our attention to utilizing other protecting groups. When the imine prepared from 4-tolualdehyde and benzyl amine was used as the electrophilic acceptor, we were pleased to find that a similar product was obtained. Interestingly, though, in the ^1H NMR spectrum the presence of an N–*H* proton was conspicuously lacking. Closer inspection showed a molecular weight of 277 amu by GC/MS analysis and a carbonyl stretching vibration of 1638 cm^{-1} in the FTIR spectrum, which is consistent with an amide, or its vinylogous analog. Such results are indicative of the formation of a benzyl-protected aza Diels–Alder product (Scheme 2).

Encouraged by these results, attention was turned to optimizing this process. Again a variety of potential Lewis acid catalysts were screened and MgI_2 was found to be optimal. Unfortunately, it was found that substoichiometric loadings of MgI_2 failed to promote the reaction to completion.[7] However, with 100% Lewis acid loading the reaction proceeded to completion in 22 h at 0 °C in CH_2Cl_2 as monitored by ^1H NMR analysis of the crude reaction mixtures. Furthermore, a 2 to 1 ratio of diene to imine was found to be favorable for reasonable reaction rates and high yields. It should be noted that a 1:1 ratio of diene to imine did not result in the complete consumption of imine even after 48 h at 0 °C. With regard to solvents, both THF and toluene work, albeit with somewhat diminished yields. Acetonitrile was found to give unsatisfactory results.

In light of the above results, the optimized reaction conditions were found to be as follows: 2.0 equiv iodosilyloxy diene (prepared by stirring 3-butyn-2-one and TMSI in dry CH_2Cl_2 at 0 °C for 30 min under an inert atmosphere) were added to benzyl-protected imine (1.0 equiv) and MgI_2 (1.0 equiv) in CH_2Cl_2 under an inert atmosphere. The reaction was stirred at 0 °C for 22 h before being quenched with 1 N HCl and subjected to standard extractive workup. The results of this reaction process utilizing a variety of benzyl-protected imines[8] are summarized in Table 1.

As can be seen from Table 1, imine substrates bearing nearly electroneutral or even strongly electron-withdrawing substituents all worked very well. On the other hand, attempts at using the imine prepared from 4-anisaldehyde, which bears the strongly electron-donating methoxy group, resulted in low conversion and the formation of only a trace amount of product. Additionally, the use of benzyl imine prepared from 2-tolualdehyde failed to result in any product at all, presumably due to unfavorable steric interactions.

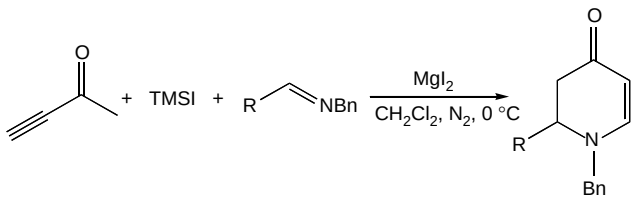
After establishing this protocol for the synthesis of *N*-benzyl aza Diels–Alder products, we then turned our attention to other *N*-protecting groups in order to explore the generality of this process. We were pleased to find that a number of imines with *N*-aromatic groups all worked well for this reaction. Furthermore, these imines were found to be more reactive, giving typically higher yields in shorter reaction



Scheme 2.

times (12 h rather than 22 h). The results are summarized in Table 2.

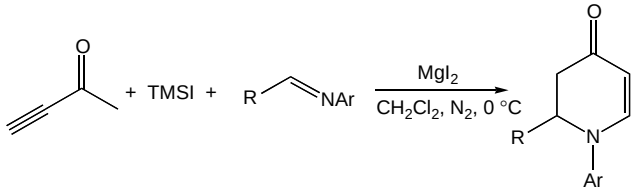
Table 1. Results of aza Diels–Alder reaction using Bn-protected imines



Entry	R	Product	Yield[a]
1	Ph–	**1a**	77
2	4-Me-C_6H_4–	**2a**	84
3	4-CF_3–C_6H_4–	**3a**	91
4	4-NO_2–C_6H_4–	**4a**	88
5	4-F–C_6H_4–	**5a**	86
6	4-Cl–C_6H_4–	**6a**	85
7	4-Br–C_6H_4–	**7a**	79

[a] Yield of pure product after column chromatography.

Table 2. Results of aza Diels–Alder reaction using aromatic protecting groups



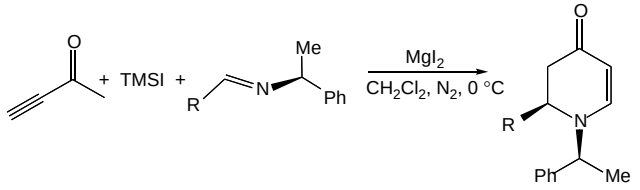
Entry	R	Ar	Product	Yield[a]
1	Ph–	Ph–	**1b**	87
2	4-Cl–C_6H_4–	Ph–	**6b**	90
3	4-Cl–C_6H_4–	4-Br–C_6H_4–	**6c**	94
4	4-Cl–C_6H_4–	4-MeO–C_6H_4–	**6d**	94

[a] Yield of pure product after column chromatography.

Due to the large demand for chiral heterocyclic building blocks, efficient routes to asymmetric dihydropyridones are quite important in organic chemistry. Several chiral catalysts were screened with the hopes of developing an enantioselective aza Diels–Alder reaction. Binol–$TiCl_2$ complex alone failed to produce any desired Diels–Alder product. Interestingly, both isopropyl-Pybox/MgI_2 complex and isopropyl-Pybox/Cu(OTf)$_2$ complex failed to promote the aza Diels–Alder reaction with benzyl imines, but both did effectively promote the reaction with aromatic-protected imines. Unfortunately, the products from both reactions were racemic. Interestingly, the use of BinolBOPh[2b] did result in the formation of the product in $<40\%$ yield, but no enantioselectivity was observed. With these results in hand, attention was then turned to focus on chiral auxiliary-controlled processes.

To date, the majority of diastereomerically controlled aza Diels–Alder reactions have been performed utilizing chiral imines derived from sugars,[9] amino esters,[10] or chiral amino alcohols.[11] Unfortunately, these products often suffer from the difficulty in removing the protecting group. With this in mind, we sought to extend the scope of this reaction to substrates bearing chiral auxiliaries that are easily removed. Initial attempts at utilizing the chiral *p*-tolylsulfinyl protecting group repeatedly resulted in no reaction. In all instances starting materials were quantitatively recovered intact. We then turned our attention to the simpler chiral imines derived from (*S*)-α-methylbenzyl amine since this type of imine bears a strong resemblance to the benzyl protected imines. Fortunately, when the corresponding imine prepared from benzaldehyde was utilized, the two possible diastereomers were isolated in moderate yield. Furthermore, the two diastereomers, obtained in a 3:1 ratio, were readily separated and isolated in diastereomerically pure form by column chromatography.[12] In light of these results, several chiral imines were prepared and subjected to these conditions. The results are summarized in Table 3.

Table 3. Results of diastereoselective aza Diels–Alder reaction



Entry	R	Product	Diastereo-selectivity[a]	Yield[b]
1	Ph–	**1e**	3:1	61
2	4-CF_3–C_6H_4–	**3e**	3:1	84
3	4-Cl–C_6H_4–	**6e**	3:1	72
4	*n*-Pr–	**8e**	4.5:1	62
5	3-NO_2–C_6H_4–	**9e**	4:1	82
6	2,4-(NO_2)$_2$–C_6H_3–	**10e**	4:1	85

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Combined yield of 2 isomers after purification by column chromatography.

As can be seen from Table 3, a number of electroneutral and electron-poor substrates are tolerated in this process. Moderate diastereoselectivities were observed, however, it is important to note that all products were readily separable with standard column chromatography techniques. Of particular interest in Table 3 are entries 4 and 5, in which aliphatic and *meta*-substituted aromatic imines were successfully utilized as substrates for the aza Diels–Alder reaction. Furthermore, a 2,4-disubstituted substrate (entry 6) was also found to work well if the groups were strongly electron withdrawing. Comparison of Tables 1 and 3 demonstrates that these α-methylbenzyl imines are slightly less reactive than the corresponding benzyl imines, presumably due to increased steric bulk.

With regard to mechanism, two possibilities seem plausible. A [4+2] cycloaddition followed by elimination of iodine would constitute the typical Diels–Alder pathway. Alternatively, it has been shown in similar reactions utilizing Danishefsky's diene that such reactions occur via a Mannich/cyclization pathway.[2d,f] A mechanistic study is currently underway and relevant results will be disclosed in due course.

In summary, a new method for the synthesis of dihydropyridones has been reported. The reaction is tolerant of a variety of substrates, including *N*-benzyl- and

N-aryl-protected imines. Attempts at rendering the reaction asymmetric have been successful. Importantly, this work represents the first Diels–Alder type reaction with this new class of iodo-diene.

3. Experimental

3.1. General methods

All reactions were performed in oven-dried glassware. Dichloromethane was purified and dried via an Alumina column immediately prior to use. NMR spectra were recorded on a Varian Inova NMR spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) or on a Varian Mercury NMR spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). Shift values are reported in ppm and are referenced based on TMS or solvent for ^{1}H and ^{13}C, respectively. All spectra were recorded in $CDCl_3$. ^{19}F NMR spectra, where applicable, were recorded in $CDCl_3$ and shifts are reported based on an external TFA reference. Imines were prepared according to standard methods. All other commercially available chemicals were used without further purification and stoichiometries were calculated by the purities reported by the manufacturers. Purification was performed by flash chromatography on silica gel (Merck 60, 230–400 mesh). IR spectra were recorded as CH_2Cl_2 deposits on a NaCl disk. Unless otherwise indicated, optical rotations were performed in CH_2Cl_2 with a concentration of 0.5.

3.2. Procedure for the aza Diels–Alder reaction

Into a dried, N_2 flushed vial was added CH_2Cl_2 (2.0 mL), 3-butyn-2-one (1.1 mmol), and iodotrimethylsilane (1.0 mmol) at 0 °C. Concurrently, into another dried, N_2 flushed vial containing 0.5 mmol MgI_2 was added imine (0.5 mmol) and 2 mL CH_2Cl_2. Both vials were stirred for 30 min at 0 °C, at which time the contents of the first vial were transferred to the second via syringe. The reaction was stirred at 0 °C under N_2 atmosphere until completion was observed by ^{1}H NMR analysis, at which time it was quenched with 5 mL 1 M HCl. The mixture was extracted with CH_2Cl_2, washed with brine, and dried over anhydrous Na_2SO_4. The crude extract was concentrated to dryness and directly subjected to column chromatography (EtOAc/hexane, 1:3→3:1) to afford the pure product.

3.3. Spectroscopic data

3.3.1. *N*-Benzyl-2,3-dihydro-2-phenyl-4-pyridone (1a). This is a known compound. ^{1}H NMR spectral data are consistent with literature values.[2b] ^{1}H NMR (300 MHz, $CDCl_3$): 7.40–7.10 (m, 11H), 5.08 (d, J=7.8 Hz, 1H), 4.50 (t, J=7.5 Hz, 1H), 4.35 (d, J=15.3 Hz, 1H), 4.13 (d, J=15.0 Hz, 1H), 2.85 (dd, J=7.2, 16.5 Hz, 1H), 2.68 (dd, J=7.8, 16.5 Hz, 1H).

3.3.2. *N*-Benzyl-2,3-dihydro-2-(4-methylphenyl)-4-pyridone (2a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.37–7.30 (m, 3H), 7.27 (d, J=8.0 Hz, 1H), 7.17–7.12 (m, 6H), 5.08 (d, J=7.5 Hz, 1H), 4.46 (t, J=7.5 Hz, 1H), 4.32 (d, J=15 Hz, 1H), 4.12 (d, J=15.5 Hz, 1H), 2.80 (dd, J=7.0, 16.5 Hz, 1H), 2.68 (dd, J=8.5, 16.5 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.6, 154.1, 138.1, 136.0, 135.6, 129.7, 128.9, 128.2, 127.7, 127.1, 98.7, 60.5, 57.1, 43.8, 21.1. FTIR: 1638.0 cm^{-1}. GC/MS: m/z=277 (M^+, 91%), 249 (25%), 186 (26%), 118 (74%), 91 (100%). Calculated for $C_{19}H_{19}NO$: M^+=277.

3.3.3. *N*-Benzyl-2,3-dihydro-2-(4-trifluoromethylphenyl)-4-pyridone (3a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.63–7.60 (m, 2H), 7.39–7.32 (m, 6H), 7.15–7.13 (m, 2H), 5.11 (d, J=7.5 Hz, 1H), 4.56 (t, J=7.5 Hz, 1H), 4.40 (d, J=15 Hz, 1H), 4.12 (d, J=15 Hz, 1H), 2.90 (dd, J=7.0, 16.5 Hz, 1H), 2.62 (dd, J=7.0, 16.5 Hz, 1H). ^{19}F NMR (212.3 MHz, $CDCl_3$): −63.06 (s). ^{13}C NMR (125 MHz, $CDCl_3$): 189.5, 153.9, 142.6, 135.5, 130.6 (q, J=32.1 Hz), 129.1, 128.4, 127.7, 127.4, 126.0 (q, J=1.9 Hz), 123.8 (q, J=270.5 Hz), 99.1, 60.0, 43.3. FTIR: 1638.9 cm^{-1}. HRMS MH^+: expected: 332.1257 found: 332.1266.

3.3.4. *N*-Benzyl-2,3-dihydro-2-(4-nitrophenyl)-4-pyridone (4a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.23–8.20 (m, 2H), 7.44–7.41 (m, 2H), 7.37–7.34 (m, 4H), 7.15–7.13 (m, 2H), 5.13 (d, J=7.5 Hz, 1H), 4.61 (t, J=7.0 Hz, 1H), 4.44 (d, J=15 Hz, 1H), 4.12 (d, J=15 Hz, 1H), 2.93 (dd, J=7.0, 16.5 Hz, 1H), 2.61 (dd, J=7.0, 16.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.0, 153.8, 147.8, 145.9, 135.2, 129.1, 128.6, 127.9, 127.6, 124.3, 99.4, 59.7, 57.9, 43.0. FTIR: 1637.5 cm^{-1}. HRMS MH^+: expected: 309.1234 found: 309.1224.

3.3.5. *N*-Benzyl-2,3-dihydro-2-(4-fluorophenyl)-4-pyridone (5a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.31 (m, 3H), 7.29 (d, J=7.5 Hz, 1H), 7.23–7.20 (m, 2H), 7.13–7.10 (m, 2H), 7.06–7.01 (m, 2H), 5.09 (d, J=7.5 Hz, 1H), 4.48 (t, J=7.5 Hz, 1H), 4.35 (d, J=15 Hz, 1H), 4.01 (d, J=15.5 Hz, 1H), 2.83 (dd, J=7.0, 16.5 Hz, 1H), 2.64 (dd, J=7.5, 16.5 Hz, 1H). ^{19}F NMR (212.3 MHz, $CDCl_3$): −113.86 (m). ^{13}C NMR (125 MHz, $CDCl_3$): 190.1, 162.5 (d, J=245.9 Hz), 154.1, 135.7, 134.4 (d, J=3.4 Hz), 129.0, 128.8, 128.6 (d, J=68.6 Hz), 127.6, 115.9 (d, J=21.6 Hz), 98.8, 59.9, 57.3, 43.7. FTIR: 1637.9 cm^{-1}. HRMS MH^+: expected: 282.1289 found: 282.1290.

3.3.6. *N*-Benzyl-2,3-dihydro-2-(4-chlorophenyl)-4-pyridone (6a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.31 (m, 5H), 7.29 (d, J=7.5 Hz, 1H), 7.20–7.17 (m, 2H), 7.14–7.11 (m, 2H), 5.09 (d, J=7.5 Hz, 1H), 4.47 (t, J=7.5 Hz, 1H), 4.36 (d, J=15.5 Hz, 1H), 4.10 (d, J=15 Hz, 1H), 2.83 (dd, J=7.0, 16.5 Hz, 1H), 2.62 (dd, J=8.0, 16.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.9, 154.0, 137.1, 135.6, 134.1, 129.2, 129.0, 128.5, 128.3, 127.7, 99.0, 59.9, 57.4, 43.5. FTIR: 1637.7 cm^{-1}. HRMS MH^+: expected: 298.0993 found: 298.0988.

3.3.7. *N*-Benzyl-2,3-dihydro-2-(4-bromophenyl)-4-pyridone (7a). Isolated as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.50–7.47 (m, 2H), 7.38–7.33 (m, 3H), 7.29 (d, J=7.5 Hz, 1H), 7.14–7.11 (m, 4H), 5.09 (d, J=8.0 Hz, 1H), 4.46 (t, J=7.5 Hz, 1H), 4.36 (d, J=15.5 Hz, 1H), 4.10 (d, J=15 Hz, 1H), 2.83 (dd, J=7.0, 16.5 Hz, 1H), 2.62 (dd, J=8.0, 16.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.9,

154.0, 137.6, 135.6, 132.2, 129.0, 128.8, 128.3, 127.7, 122.2, 99.0, 60.0, 57.4, 43.5. FTIR: 1637.7 cm^{-1}. HRMS MH^+: expected: 342.0488 found: 342.0477.

3.3.8. *N*-Phenyl-2,3-dihydro-2-phenyl-4-pyridone (1b). This is a known compound. ^1H NMR spectral data are consistent with literature values.[2g] ^1H NMR (500 MHz, $CDCl_3$): 7.68 (dd, $J=1.0$, 7.5 Hz, 1H), 7.34–7.26 (m, 7H), 7.12–7.09 (m, 1H), 7.03–7.01 (m, 2H), 5.30–5.27 (m, 2H), 3.31 (dd, $J=7.5$, 16.5 Hz, 1H), 2.79 (ddd, $J=1.0$, 3.0, 16.5 Hz, 1H).

3.3.9. *N*-Phenyl-2,3-dihydro-2-(4-chlorophenyl)-4-pyridone (6b). This is a known compound. ^1H NMR spectral data are consistent with literature values.[2g] ^1H NMR (500 MHz, $CDCl_3$): 7.65 (dd, $J=1.0$, 7.5 Hz, 1H), 7.33–7.29 (m, 4H), 7.22–7.19 (m, 2H), 7.14–7.11 (m, 1H), 7.05–6.99 (m, 2H), 5.29 (dd, $J=1.0$, 8.0 Hz, 1H), 5.26 (dd, $J=3.0$, 7.0 Hz, 1H), 3.29 (dd, $J=7.5$, 16.5 Hz, 1H), 2.74 (ddd, $J=1.0$, 3.5, 16.5 Hz, 1H).

3.3.10. *N*-(4-Bromophenyl-2,3-dihydro-2-(4-chlorophenyl)-4-pyridone (6c). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 7.58 (dd, $J=1.0$, 8.0 Hz, 1H), 7.42–7.40 (m, 2H), 7.32–7.29 (m, 2H), 7.19–7.17 (m, 2H), 6.89–6.85 (m, 2H), 5.31 (dd, $J=0.5$, 8.0 Hz, 1H), 5.21 (dd, $J=3.0$, 7.0 Hz, 1H), 3.27 (dd, $J=7.0$, 16.5 Hz, 1H), 2.75 (ddd, $J=1.0$, 3.0, 16.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.7, 147.5, 143.5, 136.1, 134.0, 132.6, 129.4, 127.5, 120.1, 117.5, 103.8, 61.2, 43.3. FTIR: 1650.4 cm^{-1}. HRMS MH^+: expected: 361.9942 found: 361.9933.

3.3.11. *N*-(4-Methoxyphenyl-2,3-dihydro-2-(4-chlorophenyl)-4-pyridone (6d). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 7.52 (dd, $J=1.0$, 7.5 Hz, 1H), 7.29–7.26 (m, 2H), 7.21–7.19 (m, 2H), 6.95–6.92 (m, 2H), 6.83–6.80 (m, 2H), 5.23 (dd, $J=1.0$, 7.5 Hz, 1H), 5.16 (dd, $J=4.0$, 7.0 Hz, 1H), 3.77 (s, 3H), 3.24 (dd, $J=7.5$, 16.5 Hz, 1H), 2.72 (ddd, $J=1.0$, 4.0, 16.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): 189.7, 157.0, 149.5, 138.1, 136.8, 133.7, 129.1, 127.8, 121.2, 114.7, 101.8, 61.9, 55.5, 43.3. FTIR: 1646.6 cm^{-1}. HRMS MH^+: expected: 314.0942 found: 314.0936.

3.3.12. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-phenyl-4-pyridone (1e). This is a known compound. ^1H NMR spectral and optical rotation data are consistent with literature values.[2b] ^1H NMR (300 MHz, $CDCl_3$): 7.26–7.45 (m, 10H), 7.04 (d, $J=7.8$ Hz, 1H), 5.04 (d, $J=7.8$ Hz, 1H), 4.70 (dd, $J=6.6$, 9.0 Hz, 1H), 4.43 (q, $J=6.9$ Hz, 1H), 2.82 (dd, $J=6.9$, 16.5 Hz, 1H), 2.71 (dd, $J=9.0$, 16.5 Hz, 1H), 1.47 (d, $J=6.9$ Hz, 3H). $[\alpha]_D^{24}$: lit: −181.7, Found: −177.8 (*c* 1.7, $CHCl_3$).

3.3.13. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-(4-trifluoromethylphenyl)-4-pyridone (3e). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 7.62 (d, $J=8.0$ Hz, 2H), 7.49 (d, $J=8.0$ Hz, 2H), 7.41–7.38 (m, 2H), 7.36–7.32 (m, 1H), 7.29–7.27 (m, 2H), 7.16 (d, $J=7.5$ Hz, 1H), 5.06 (d, $J=7.5$ Hz, 1H), 4.73 (dd, $J=7.0$, 7.0 Hz, 1H), 4.47 (q, $J=7.0$ Hz, 1H), 2.89 (dd, $J=7.0$, 16.5 Hz, 1H), 2.59 (dd, $J=7.0$, 16.5 Hz, 1H), 1.49 (d, $J=7.0$ Hz, 3H). ^{19}F NMR (212.3 MHz, $CDCl_3$): −63.06 (s). ^{13}C NMR (125 MHz, $CDCl_3$): 189.5, 151.8, 143.7, 139.5, 130.5 (q, $J=32.6$ Hz), 129.0, 128.4, 127.3, 127.2, 126.1 (q, $J=3.9$ Hz), 123.8 (q, $J=270.5$ Hz), 99.9, 60.5, 59.6, 43.6, 17.9. FTIR: 1637.9 cm^{-1}. $[\alpha]_D^{24}$ −90.4. HRMS MH^+: expected: 346.1413 found: 346.1410.

3.3.14. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-(4-chlorophenyl)-4-pyridone (6e). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 7.40–7.31 (m, 7H), 7.28–7.26 (m, 2H), 7.09 (d, $J=7.5$ Hz, 1H), 5.04 (d, $J=7.5$ Hz, 1H), 4.66 (dd, $J=7.0$, 7.0 Hz, 1H), 4.44 (q, $J=7.0$ Hz, 1H), 2.82 (dd, $J=7.0$, 16.5 Hz, 1H), 2.61 (dd, $J=8.0$, 16.5 Hz, 1H), 1.47 (d, $J=7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.9, 151.8, 139.6, 138.1, 134.1, 129.3, 128.9, 128.3, 1228.2, 127.3, 99.8, 59.83, 59.80, 43.9, 17.7. FTIR: 1637.6 cm^{-1}. $[\alpha]_D^{24}$ −175.5. HRMS MH^+: expected: 312.115 found: 312.1144.

3.3.15. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-*n*-propyl-4-pyridone (8e). This is a known compound.[2b] ^1H NMR spectral and optical rotation data are consistent with literature values. ^1H NMR (300 MHz, $CDCl_3$): 7.50–7.30 (m, 5H), 6.90 (d, $J=7.2$ Hz, 1H), 4.87 (d, $J=7.2$ Hz, 1H), 4.56 (q, $J=6.9$ Hz, 1H), 3.51–3.61 (m, 1H), 2.68 (dd, $J=6.6$, 16.2 Hz, 1H), 2.32 (dd, $J=2.7$, 16.2 Hz, 1H), 2.10–1.90 (m, 1H), 1.66 (d, $J=6.9$ Hz, 3H), 1.52–1.20 (m, 3H), 0.92 (t, $J=7.2$ Hz, 3H). $[\alpha]_D^{24}$: lit: +163.1, Found: +161.8 (*c* 1.0, $CHCl_3$).

3.3.16. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-(3-nitrophenyl)-4-pyridone (9e). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 8.17–8.15 (m, 2H), 7.69–7.67 (m, 1H), 7.56–7.51 (m, 1H), 7.41–7.33 (m, 3H), 7.29–7.27 (m, 3H), 5.09 (d, 1H, $J=8.0$ Hz), 4.77 (dd, 1H, $J=5.5$, 7.0 Hz), 4.54 (q, 1H, $J=7.0$ Hz), 2.95 (dd, 1H, $J=7.5$, 16.5 Hz), 2.55 (dd, 1H, $J=5.5$, 16.5 Hz), 1.52 (d, 3H, $J=7.0$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): 188.8, 151.6, 148.5, 141.8, 139.3, 132.7, 130.2, 129.0, 128.5, 127.1, 123.1, 121.8, 99.9, 61.4, 58.8, 43.2, 18.3. FTIR: 1637.9 cm^{-1}. $[\alpha]_D^{24}$ −69.2. HRMS MCl^-: expected: 357.1011 found: 357.1017.

3.3.17. (2*R*)-2,3-Dihydro-*N*-(*S*)-α-methylbenzyl-2-(2,4-dinitrophenyl)-4-pyridone (10e). Isolated as an oil. ^1H NMR (500 MHz, $CDCl_3$): 8.74 (d, 1H, $J=2.5$ Hz), 8.32 (dd, 1H, $J=2.5$, 9.0 Hz), 7.92 (d, 1H, $J=8.5$ Hz), 7.44 (dd, 1H, $J=1.0$, 7.5 Hz), 7.36–7.29 (m, 3H), 7.20–7.19 (m, 2H), 5.48 (dd, 1H, $J=2.5$, 9.0 Hz), 5.12 (dd, 1H, $J=1.0$, 8.0 Hz), 4.54 (q, 1H, $J=7.0$ Hz), 3.13 (dd, 1H, $J=9.0$, 17.0 Hz), 2.43 (dd, 1H, $J=2.5$, 17.0 Hz), 1.54 (d, 3H, $J=7.0$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): 180.1, 151.4, 147.4, 147.3, 141.9, 138.9, 130.5, 129.2, 128.8, 127.2, 126.8, 120.7, 99.4, 63.2, 53.9, 41.3, 18.9. FTIR: 1637.8 cm^{-1}. $[\alpha]_D^{24}$ −195.0. HRMS MH^+: expected: 368.1241 found: 368.1232.

Acknowledgements

We gratefully acknowledge financial support from the National Institutes of Health (CA 99995-1) and the Robert A. Welch Foundation (D-1361).

References and notes

1. (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) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
2. (a) Kerwin, J. F.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 3739. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749. (c) Creswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppen, M. *Tetrahedron* **1998**, *54*, 3983. (d) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309. (e) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574. (f) Mancheno, O. G.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. (g) Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6163.
3. (a) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569. (b) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855. (c) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469.
4. (a) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240. (b) Sebesta, R.; Pizzuti, M. G.; Boersma, A. J.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2005**, 1711. (c) Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 2433.
5. (a) Wei, H.-X.; Kim, S. H.; Li, G. *Org. Lett.* **2002**, *4*, 3691. (b) Wei, H.-X.; Timmons, C.; Garag, M. A.; Pare, P. W.; Li, G. *Org. Biomol. Chem.* **2004**, *2*, 2893.
6. (a) Timmons, C.; Chen, D.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 2075. (b) Timmons, C.; Guo, L.; Liu, J.; Cannon, J. F.; Li, G. *J. Org. Chem.*, **2005**, *70*, 76–84.
7. Reactions of this type are known to frequently require stoichiometric loadings of Lewis acid promoter. See Ref. 1c.
8. Imines were prepared under standard conditions by mixing aldehyde, amine, and $MgSO_4$ in benzene. See Ref. 2b and references therein.
9. (a) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed.* **1989**, *28*, 1067. (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158.
10. (a) Larsen, S. D.; Greico, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Waldmann, H. *Synlett* **1995**, 133.
11. Devine, P. N.; Reilly, M.; Oh, T. *Tetrahedron Lett.* **1993**, *34*, 5827.
12. The absolute structure was determined by comparison with a known compound. See Ref. 2b.