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Catalytic Staudinger/Aza-Wittig Sequence by in situ Phosphane Oxide Reduction

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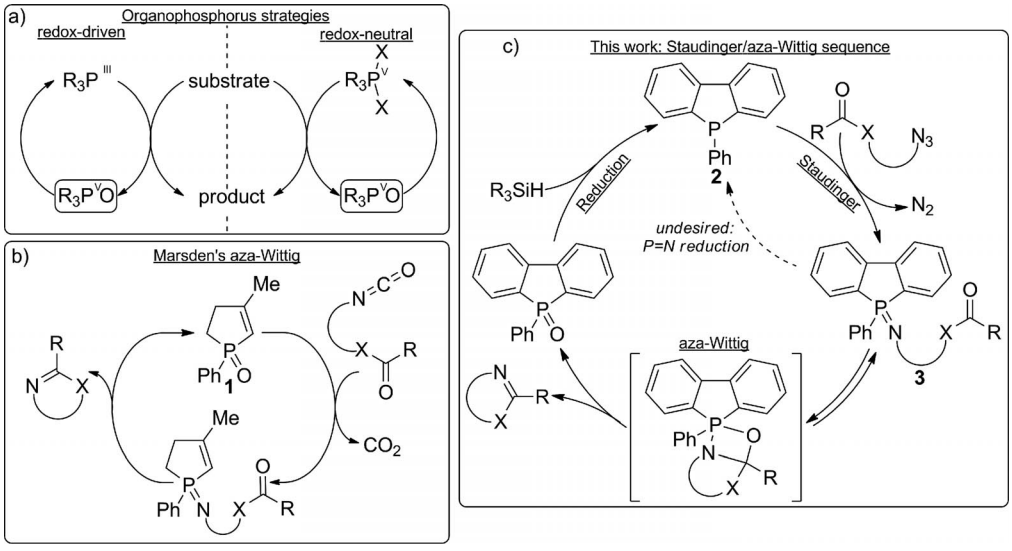
A Staudinger/aza-Wittig reaction sequence is described that is catalytic in phosphorus. Towards this end, the phosphane oxide is reduced in situ by diphenylsilane, which allows for substoichiometric amounts of the catalyst 5-phenyldibenzophosphole to be used. The substrate scope is investigated and benzoxazoles, benzodiazepine imidates and a 2-methoxypyrrole were successfully synthesized. These investigations show that a fast aza-Wittig reaction is required to obtain high yields.

Introduction

The aza-Wittig reaction has proven extremely effective for constructing C=N bonds from ketones or aldehydes and is particularly effective for making (aromatic) heterocycles.[1] However, as with most phosphane-consuming reactions, the phosphane oxide side product can be problematic during product purification and lowers the atom economy of the reaction. Although elegant solutions exist to address the purification issue, the atom economy of the reaction can only be improved by using catalytic phosphane reagent.[2]

In the last decade, significant progress has been made in the development of catalytic organophosphorus-based reactions that typically require stoichiometric amounts of phosphane.[3] Two different approaches to achieve such a goal can be identified, i) a redox-neutral or ii) a redox-driven approach (Scheme 1, a). The redox-neutral approach was (re)introduced by Marsden et al. for an intramolecular aza-Wittig reaction, by reacting a substrate containing both an



Scheme 1. a) Organophosphorus strategies by either redox-driven or redox neutral strategies; b) the aza-Wittig as developed by Marsden et al. via the redox neutral reaction pathway; c) the proposed mechanistic cycle for the Staudinger/aza-Wittig sequence as presented in this paper.

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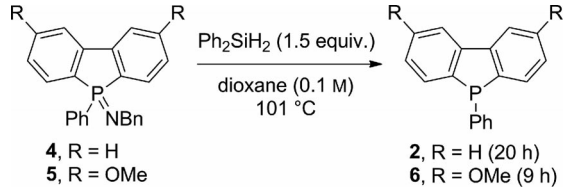
ester and an isocyanate function in the presence of catalytic phospholane oxide **1** (Scheme 1, b).[4] In this process, it is postulated that reaction of isocyanate with phospholane oxide **1** leads to an iminophosphorane intermediate that undergoes intramolecular aza-Wittig reaction with the ester moiety thus liberating the desired C=N-product. Another redox-neutral strategy has also been used by Denton et al. for catalytic Appel reactions and nitrile synthesis.[5]

The redox-driven approach, as introduced by O'Brien, involves "classical" formation of a pentavalent P^V-phosphorus compound from a P^{III}-species. However, in this case the P^{III}-compound is regenerated in situ by reduction of P^V with a suitable silane.[6] We had previously reported that the Staudinger reduction can be rendered catalytic in phosphane based on in situ reduction of the formed iminophosphorane.[6e] Because the latter iminophosphorane can, in principle, also react with a carbonyl functionality in an aza-Wittig fashion, we envisioned that a catalytic Staudinger/aza-Wittig sequence should be feasible. As visualized in Scheme 1 (c), such a tandem sequence should involve intramolecular reaction of intermediate dibenzophosphole-based iminophosphorane **3** with an ester moiety prior to reduction. Notably, such a strategy requires only stable starting materials, which compares favorably with the earlier reported isocyanates. In this paper we describe the synthesis of benzoxazoles, benzodiazepine imidates and a 2-methoxypyrrole, all from azide-containing esters, by virtue of a catalytic Staudinger/aza-Wittig protocol.

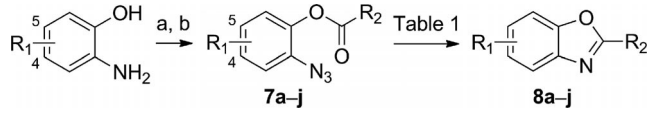
Benzoxazole Synthesis

In considering Scheme 1 (c) it became clear that the iminophosphorane preferentially reacts exclusively with the carbonyl moiety although we recognized the competing P=N bond reduction (i.e. Staudinger reduction[6e]), as a potential pitfall. Consequently, we first investigated the relative reduction rate of iminophosphoranes based on our previously developed organophosphorus catalysts **2** and **6**. We had previously established that reduction of the corresponding oxides of dibenzophosphole **2** and **6** is fast enough to achieve catalytic turnovers. As a result, both **2** and **6** constituted suitable candidates for catalytic Staudinger/aza-Wittig reaction. At the same time, we realized that reduction of the P=N bond should be minimal under these conditions in order to enable the desired reaction of the iminophosphorane intermediate with the carbonyl group. To this end, iminophosphoranes **4** and **5** were individually subjected to reduction with diphenylsilane (1.5 equiv.) in [D_8]dioxane at 101 °C. We observed a faster P=N bond reduction of methoxy-substituted **5** with respect to **4** and thus decided to continue our investigations with **2** (R = H)[7] (Scheme 2).

Our first focus, when performing intramolecular aza-Wittig reactions, was on the synthesis of benzoxazoles, a class of compounds featured in natural products,[8] pharmaceutically relevant compounds[9] and functional materials to name just a few.[10] Currently, there are two distinct methods for the synthesis of benzoxazoles from aminophenols. One approach involves direct reaction with carboxylic acids mediated by strong acids[11] or high temperatures under microwave irradiation.[12] The alternative approach relies on reaction of the amino group with an aldehyde, to form an intermediate imine that subsequently undergoes oxidative cyclization.[13] An aza-Wittig reaction might offer milder conditions and higher selectivity compared to the established methods. More importantly, we envisioned that benzoxazole precursors could effectively be used to investigate the influence of different substituents on the rate of P=N bond reduction vs. aza-Wittig cyclization. The requisite starting materials were readily obtained from commercially available compounds by a two-step procedure composed of i) initial formation of 2-azidophenol by diazotization and nucleophilic aromatic substitution with sodium azide, followed by ii) acylation with an acid chloride (Scheme 3).



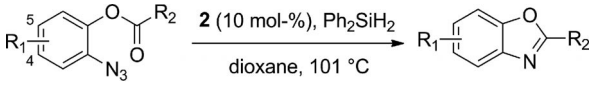
Scheme 2. Reduction of iminophosphoranes **4** and **5** by Ph_2SiH_2. Reactions (0.1 M in [D_8]dioxane, 101 °C) were monitored by ^{31}P NMR spectroscopy.



Scheme 3. Substrate synthesis for catalytic Staudinger/aza-Wittig sequence. a) HCl, $NaNO_2$ at 0 °C in H_2O, then NaN_3 at r.t.; b) Et_3N, DMAP and R_2COCl at 0 °C in DCM.

With both the desired catalyst and substrates in hand, the stage was set for selection of a suitable reagent for the in situ phosphane oxide reduction. Two common reagents used to effect such transformations are diphenylsilane and phenylsilane. Consequently, 2-azidophenyl benzoate (**7a**) and dibenzophosphole **2** (10 mol-%) were treated with each of these reductants to induce a catalytic Staudinger/aza-Wittig reaction (Table 1). The use of the stronger reducing agent phenylsilane afforded much less product (50%, not shown) than was obtained using the milder diphenylsilane (Table 1, Entry 1, 74%). This result was an indication that competitive P=N bond reduction was a significant consideration. Hence, diphenylsilane was selected as the reductant of choice for further use. As a reference, the reaction with a stoichiometric amount (1.1 equiv.) of dibenzophosphole **2** proceeded similarly (74% yield, not shown). In the absence of a silane reductant, only 10% conversion to the product was observed by NMR (not shown).

Table 1. Benzoxazole synthesis using the catalytic Staudinger/aza-Wittig reaction.



7a–j 8a–j

Entry	R_1	R_2	Product	Time [h]	Yield[a] [%]
1	H	Ph	**8a**	24	74[b]
2	H	4-$MeOC_6H_4$	**8b**	24	95
3	H	4-$F_3CC_6H_4$	**8c**	48	66
4	H	4-PhC_6H_4	**8d**	24	70
5	H	Me	**8e**	24	59[c]
6	H	*t*Bu	**8f**	24	80
7	5-OMe	Ph	**8g**	22	54
8	4-OMe	Ph	**8h**	24	55
9	4-NO_2	Ph	**8i**	44	53
10	5-Cl	Ph	**8j**	44	55
11	5-Cl	Ph	**8j**	44	65[d]
12	5-Cl	Ph	**8j**	6	84[e]

[a] Isolated yields. [b] 50% yield in case reaction is performed with $PhSiH_3$. [c] Volatility of the product lowered the isolated yield, GC yield was 80% (corrected by internal standard). [d] Ph_2SiH_2 was added by pump over 24 h. [e] 35 mol-% **2** was used.

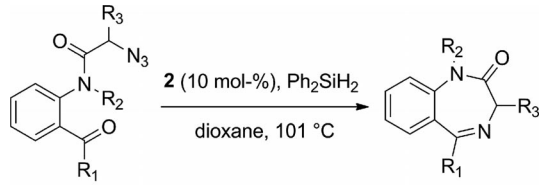
To investigate the effect of variations in the acyl moiety (R_2), several structural analogues of **7** were heated in the presence of **2** and diphenylsilane. It became clear that an electron-donating substituent on the ester moiety has a positive effect on the aza-Wittig reaction (Table 1, Entry 2, 95%) whereas electron-withdrawing groups at the same position diminish yields (Table 1, Entry 3, 66%). Different alkyl esters gave good conversions to the corresponding benzoxazoles (Table 1, Entries 5 and 6). In the absence of phosphane, the starting materials did not show any reaction with the silane reducing agent and we therefore hypothesize that electron-withdrawing substituents diminish rates of phosphane oxide elimination, thereby paving the way for reversible P=N bond formation and subsequent reduction (Scheme 1, c).[14] Such a mechanism also explains the apparent discrepancy of our observations with those of Johnson et al., who had reported earlier that electron-withdrawing substituents on aromatic aldehydes accelerate intermolecular aza-Wittig reactions.[15a] It may be argued that, in this case, the rate-limiting step is (bimolecular) nucleophilic attack of the iminophosphorane onto the aldehyde, which is facilitated by electron-withdrawing effects.

In contrast to the influence of different esters, variations in the azide-containing aryl ring (R_1) led only to modest yields for both electron-donating and withdrawing substituents (Table 1, Entries 7–10). Although it is known that the reactivity of iminophosphoranes in aza-Wittig reactions are influenced by the polarity of the P=N bond and the basicity of the system,[15] an electron-donating substituent like OMe might increase the Lewis basicity of the P=N bond and thereby also increase the reduction rate; such an effect is known for phosphane oxides.[6c] An electron-withdrawing substituent such as the nitro group (Table 1, Entry 9) or chloride (Table 1, Entry 10) might decrease the aza-Wittig cyclization rate thus indirectly promoting P=N reduction. Such an effect would be similar to that seen with an electron-withdrawing substituent on the aryl ester. Indeed, a higher yield could be obtained by suppressing P=N bond reduction by maintaining a lower silane concentration through slow addition over time (Table 1, Entry 11). Furthermore, a remarkably high yield was obtained with a higher (35 mol-%) catalyst loading (Table 1, Entry 12).

Benzodiazepines

After establishing the potential of the catalytic Staudinger/aza-Wittig protocol for benzoxazole production, we shifted our focus to the synthesis of seven-membered benzodiazepines. This was stimulated by the fact that benzodiazepines are the core structure of pharmaceutically significant agents such as diazepam, midazolam, nitrazepam and triazolam. Hence, we initially focused on the synthesis of substituted variants of the core structure, 1,4-benzodiazepin-2-ones (**10**), of these particular compounds (Table 2). By applying the optimized conditions for the aza-Wittig reaction, we successfully obtained product **10a** from azidoketone **9a** (Table 2, Entry 1) in excellent yield. However, in this particular case it cannot be excluded that an intermediate silylamine, formed by the competing P=N bond reduction, cyclizes to the imine product by straightforward condensation. In the case of ester analogues **9b**–**d**, such direct nucleophilic attack of an intermediate amine would lead to amide formation instead of the desired imidates **10b**–**d**. Thus, the reaction pathway for these particular substrates is apparent based on the type of product formed. Unfortunately, cyclization of **9b**, a secondary amide, failed to yield any detectable product; neither desired imidate nor the corresponding amide could be observed in a complex mixture of products (Table 2, Entry 2). Methylated derivative of **9b**, [**9c** (R_2 = Me, Table 2, Entry 3)], did however, afford desired 5-methoxy-1,4-benzodiazepin-2-one **10c** following an aza-Wittig transformation, presumably as a consequence of facilitated *s-cis*/*trans* isomerization around the amide bond. Increasing the steric hindrance and the C(O)–

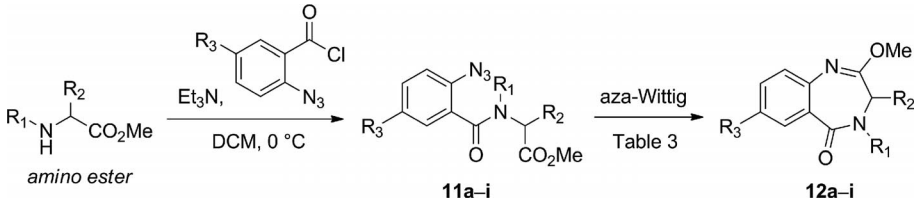
Table 2. Synthesis of 3*H*-1,4-benzodiazepin-2(1*H*)-ones **8** by application of the Staudinger/aza-Wittig protocol.



9a–d 10a–d

Entry	Substrate	R_1	R_2	R_3	Product	Time [h]	Yield[a] [%]
1	**9a**	Ph	H	H	**10a**	16	88
2	**9b**	OMe	H	H	**10b**	16	–
3	**9c**	OMe	Me	H	**10c**	16	60
4	**9d**	OMe	Me	Ph	**10d**	16	–

[a] Isolated yields.



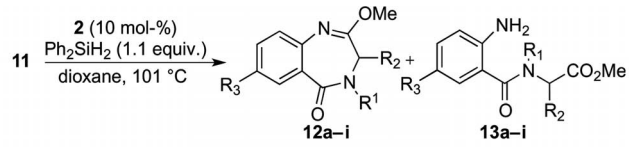
Scheme 4. Synthetic pathway to obtain 2-alkoxy-3*H*-1,4-benzodiazepin-5(4*H*)-ones (**10**) from amino esters by acylation and subsequent aza-Wittig cyclization.

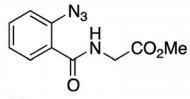
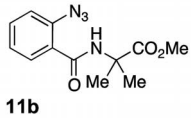
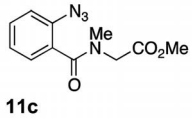
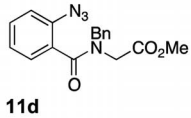
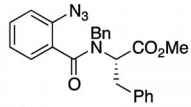
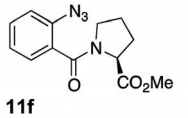
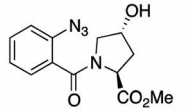
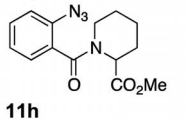
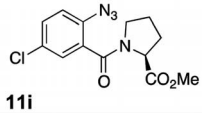
CR_3 rotation barrier near the azide group by a phenyl substituent (R_3 = Ph, Table 2, Entry 4) led to a slower aza-Wittig cyclization and resulted in a complex mixture of products. In passing, we note that **10c** is a structural variation of the previously noted pharmaceutical compounds; similar imidates have also shown biological activities with implications to the central nervous system.[16]

We also investigated the synthesis of isomeric 2-alkoxy-3*H*-1,4-benzodiazepin-5(4*H*)-ones (**12a**–**i**) from corresponding azido esters **11**, which are readily obtained by reaction of amino ester with 2-azidobenzoyl chlorides (Scheme 4). The synthesis of 2-alkoxy-3*H*-1,4-diazepin-5(4*H*)-ones (**12**) by a stoichiometric aza-Wittig is well documented by Eguchi and co-workers. Additionally, Bräse et al. have extended the Eguchi procedure to a protocol using immobilized phosphanes.[17] It was shown that also in these cases cyclization of sterically hindered phosphanes, such as Ph_3P, would only take place for tertiary amides (R_1 = Me, Bn) and that only sterically less demanding phosphanes permit cyclization of non-substituted amides (R_1 = H) by prolonged reaction at elevated temperatures (16 h, 140 °C).

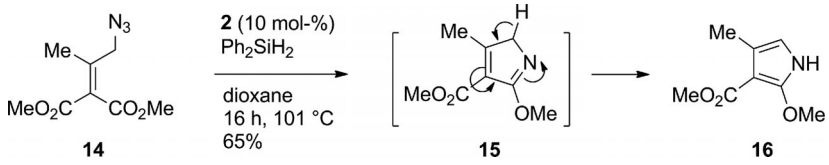
The results depicted in Table 3 show that 5-phenyldibenzophosphole (**2**) displayed similar reactivity as triphenylphosphane. No conversion was noted for the secondary amide (Table 3, Entry 1), but conversions involving tertiary amides were, indeed, observed (Table 3, Entries 3–9). It was found that a small substituent such as a methyl group, only partially induced cyclization and consequently the competing P=N bond reduction dominates the reaction. Increasing the bulkiness of the amide with a benzyl group did not improve the yield, instead leading to formation of aniline **13d** in 48% yield, confirming that P = N bond reduction is indeed a competing reaction. Similar observations were made with *gem*-dimethyl substrate **11b**, as 58% aniline **13b** was obtained (Table 3, Entry 2). However, fast cyclization took place for L-proline-derived azido ester **11f** and imidate **12f** was obtained in 81% yield (Table 3, Entry 6). Notably, no racemization occurred during the reaction sequence as confirmed by HPLC analysis. Moreover, the *trans*-2-hydroxyproline-derived azido ester **11g** reacted in 64% yield affording the desired imidate (Table 3, Entry 7). Surprisingly, reaction of the six-membered pipecolic ester derivative afforded only 7% of the cyclization product and 91% of isolated aniline **13h** (Table 3, Entry 8). Furthermore, a similar sensitivity to substituents on the aromatic system was observed as had been the case for benzoxazole formation, since a chloride at R_3 lowered the yield significantly (Table 3, Entry 9).

Table 3. Synthesis of 3*H*-1,4-benzodiazepin-5(4*H*)-ones by Staudinger/aza-Wittig protocol.



Entry	Substrate	Time (h)	Yield[a] **12** (%)	Yield[a] **13** (%)
1	 **11a**	48	0 [b]	-
2	 **11b**	25	0	58
3	 **11c**	48	23	-
4	 **11d**	70	11	48
5	 **11e**	46	10	-
6	 **11f**	16	81	-
7	 **11g**	16	64	-
8	 **11h**	72	7	91
9	 **11i**	44	21 [c]	-

[a] Isolated yields. [b] Reaction with Ph_3P gave iminophosphorane incapable of cyclization to the imidate even under prolonged heating (3 d at 140 °C). [c] Additionally, 54% dilactam was isolated, see Supporting Information.



Scheme 5. Synthesis of 2-methoxypyrrole **16** by application of the catalytic aza-Wittig protocol.

2-Methoxypyrrole

A third class of substrates that the catalytic Staudinger/aza-Wittig sequence could be suitable with is represented by 2-methoxysubstituted pyrroles (Scheme 5). In this case, treatment of azido ester **14** with **2** in the presence of diphenylsilane underwent the putative aza-Wittig cyclization to give 2*H*-pyrrole **15** as an intermediate. We hypothesize that tautomerization of **15** constituted a key transformation en route to 2-methoxy-1*H*-pyrrol **16** which was isolated in 65% yield. Importantly, the yield of **16** in our hands is nearly identical to that of a stoichiometric variation using triphenylphosphane (1.3 equiv., 60% yield), previously reported by Montforts and co-workers.[18]

Conclusions

We have successfully developed a catalytic Staudinger/aza-Wittig sequence based on in situ reduction of 5-phenyldibenzophosphole imine by diphenylsilane. The sequence can be applied to obtain a range of heterocycles from precursor azidoketones or azido esters, leading to imines or imidates, respectively. We have observed that a fast aza-Wittig cyclization is essential in order to minimize competing P=N bond reduction. In general, benzoxazoles were obtained in moderate to good yields, depending on the substitution pattern of the starting material. The pharmaceutically relevant benzodiazepines were successfully obtained when the substitution pattern promotes rapid cyclization. These examples show that organophosphorus catalysis is even possible in the presence of sensitive functional groups, such as the iminophosphorane and stimulates further study into the rapidly evolving field of catalytic phosphorus chemistry. Although diphenylsilane is probably slightly more environmentally benign than phosphane oxides,[19] the impact of the stoichiometric reagents is ideally further reduced for new catalytic reactions to be truly beneficial. Research along those lines, in particular the identification of more preferable alternatives to diphenylsilane, is currently ongoing in our laboratory.

Experimental Section

General Procedure for the aza-Wittig Reaction: The substrate (1 equiv.) was dissolved in dry dioxane (0.2 M) and diphenylsilane (1.1 equiv.) was added. Next, 5-phenyldibenzophosphole (0.1 equiv.) was added and the mixture was heated to 101 °C and stirred for the indicated time. Then, the solvent was evaporated and the crude product was purified by column chromatography (pentane/Et_2O or heptane/EtOAc).

2-Phenylbenzoxazole (8a): According to the general procedure for the aza-Wittig reaction, **7a** (50 mg, 0.21 mmol) was converted into 2-phenylbenzoxazole (60 mg, 74%) which was isolated by column chromatography (0→10% Et_2O in pentane). IR (neat): $\tilde{\nu}$ = 1553, 1448, 1242, 1053, 746, 704, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.22 (m, 2 H), 7.81–7.74 (m, 1 H), 7.62–7.55 (m, 1 H), 7.55–7.50 (m, 3 H), 7.40–7.31 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.04, 150.76, 142.11, 131.50, 128.90, 127.62, 127.18, 125.09, 124.56, 120.02, 110.58 ppm. HRMS (EI^+) calcd. for $C_{13}H_9NO$ $[M]^+$ 195.0684, found 195.0704.

Data in correspondence to commercially available compound (CAS: 833–50–1).

2-(4-Methoxyphenyl)benzoxazole (8b): According to the general procedure for the aza-Wittig reaction, **7b** (202 mg, 0.700 mmol) was converted into 2-(4-methoxyphenyl)benzoxazole (160 mg, 95%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1616, 1502, 1453, 1254, 1242, 1169, 1017, 740, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.22–8.18 (m, 2 H), 7.76–7.71 (m, 1 H), 7.57–7.53 (m, 1 H), 7.35–7.29 (m, 2 H), 7.05–7.01 (m, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.16, 162.31, 150.67, 142.28, 129.38, 124.58, 124.40, 119.71, 119.62, 114.35, 110.37, 55.45 ppm. HRMS (EI^+) calcd. for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0790, found 225.0798.

2-[4-(Trifluoromethyl)phenyl]benzoxazole (8c): According to the general procedure for the aza-Wittig reaction, **7c** (100 mg, 0.325 mmol) was converted into 2-[4-(trifluoromethyl)phenyl]-benzoxazole (57 mg, 66%) as isolated by column chromatography (0→5% Et_2O in pentane). IR (neat): $\tilde{\nu}$ = 1324, 1169, 1113, 1069, 845, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.41 (ddt, J = 3.6, 1.6, 0.8 Hz, 2 H), 7.85–7.80 (m, 3 H), 7.68–7.61 (m, 1 H), 7.46–7.39 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.49, 150.87, 141.91, 133.00 (q, J = 32.7 Hz), 130.45, 127.87, 125.94 (q, J = 3.8 Hz), 125.82, 124.96, 123.75 (q, J = 272.4 Hz), 120.42, 110.81 ppm. HRMS (FAB^+) calcd. for $C_{14}H_8F_3NO$ $[M + H]^+$ 264.0636, found 264.0630.

2-([1,1′-Biphenyl]-4-yl)benzoxazole (8d): According to the general procedure for the aza-Wittig reaction, **7d** (100 mg, 0.317 mmol) was converted into 2-([1,1′-biphenyl]-4-yl)benzoxazole (60 mg, 70%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1484, 1060, 845, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.33 (m, 1 H), 8.33–8.30 (m, 1 H), 7.83–7.74 (m, 3 H), 7.70–7.64 (m, 2 H), 7.63–7.56 (m, 1 H), 7.52–7.44 (m, 2 H), 7.43–7.32 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.92, 150.80, 144.23, 142.20, 139.99, 128.93, 128.08, 128.05, 127.55, 127.15, 125.95, 125.09, 124.59, 119.98, 110.57 ppm. HRMS (EI^+) calcd. for $C_{19}H_{13}NO$ $[M]^+$ 271.0997, found 271.0982.

2-Methylbenzoxazole (8e): According to the general procedure for the aza-Wittig reaction, **7e** (150 mg, 0.847 mmol) was converted into 2-methylbenzoxazole (66 mg, 59%) as isolated by column chromato-graphy (0→10% Et_2O in pentane) and subsequent distillation in a Kugelrohr. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.61 (m, 1 H), 7.49–7.43 (m, 1 H), 7.32–7.24 (m, 2 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.78, 150.97, 141.52, 124.41,

124.05, 119.40, 110.17, 14.50 ppm. Data in correspondence to commercially available compound (CAS: 95–21–6).

2-(*tert*-Butyl)benzoxazole (8f): According to the general procedure for the aza-Wittig reaction, **7f** (20 mg, 91 μmol) was converted into 2-(*tert*-butyl)benzoxazole (20 mg, 80%) as isolated by column chromatography (0→10% Et_2O in pentane). IR (neat): $\tilde{\nu}$ = 2972, 1610, 1564, 1455, 1293, 1251, 1243, 1125, 1121, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 1 H), 7.52–7.44 (m, 1 H), 7.32–7.25 (m, 2 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.99, 150.31, 140.76, 123.87, 123.45, 119.20, 109.80, 33.66, 27.98 ppm. HRMS (EI^+) calcd. for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.0999.

6-Methoxy-2-phenylbenzoxazole (8 g): According to the general procedure for the aza-Wittig reaction, **7g** (75 mg, 0.28 mmol) was converted into 6-methoxy-2-phenylbenzoxazole (34 mg, 54%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1618, 1485, 1448, 1143, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.17 (m, 2 H), 7.64 (dd, J = 8.8, 0.4 Hz, 1 H), 7.52–7.49 (m, 3 H), 7.12 (d, J = 2.3 Hz, 1 H), 6.96 (dd, J = 8.7, 2.4 Hz, 1 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.40, 158.45, 151.81, 136.05, 134.30, 131.22, 129.02, 127.35, 120.15, 112.97, 95.61, 56.12 ppm. HRMS (EI^+) calcd. for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0790, found 225.0766.

5-Methoxy-2-phenylbenzoxazole (8h): According to the general procedure for the aza-Wittig reaction, **7h** (50 mg, 0.19 mmol) was converted into 5-methoxy-2-benzoxazole (23 mg, 55%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1602, 1481, 1437, 1196, 1152, 705 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.25–8.22 (m, 2 H), 7.53–7.51 (m, 3 H), 7.46 (d, J = 8.8 Hz, 1 H), 7.27 (d, J = 2.5 Hz, 1 H), 6.95 (dd, J = 8.9, 2.6 Hz, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.79, 157.38, 145.41, 142.93, 131.39, 130.31, 128.88, 127.47, 113.70, 110.70, 102.88, 55.93 ppm. HRMS (EI^+) calcd. for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0790, found 225.0781.

5-Nitro-2-phenylbenzoxazole (8i): According to the general procedure for the aza-Wittig reaction, **7i** (40 mg, 0.14 mmol) was converted into 5-nitro-2-phenylbenzoxazole (18 mg, 53%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1610, 1526, 1348, 819, 735, 702, 686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (dd, J = 2.4, 0.5 Hz, 1 H), 8.31 (dd, J = 8.9, 2.3 Hz, 1 H), 8.28–8.23 (m, 2 H), 7.67 (dd, J = 8.9, 0.4 Hz, 1 H), 7.61–7.52 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.10, 154.40, 145.56, 142.69, 132.74, 129.27, 128.16, 126.08, 121.25, 116.39, 110.84 ppm. HRMS (EI^+) calcd. for $C_{13}H_8N_2O_3$ $[M]^+$ 256.0535, found 240.0543.

6-Chloro-2-phenylbenzoxazole (8j): According to the general procedure for the aza-Wittig reaction, **7j** (100 mg, 0.365 mmol) was converted into 6-chloro-2-phenylbenzoxazole (46 mg, 55%) as isolated by column chromatography (0→5% EtOAc in heptane). IR (neat): $\tilde{\nu}$ = 1449, 1331, 1051, 807, 699, 682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25–8.20 (m, 2 H), 7.67 (dd, J = 8.5, 0.4 Hz, 1 H), 7.59 (dd, J = 1.9, 0.4 Hz, 1 H), 7.57–7.49 (m, 3 H), 7.34 (dd, J = 2.0, 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.21, 150.44, 140.41, 131.31, 130.18, 128.48, 127.17, 126.23, 124.79, 119.98, 110.75 ppm. HRMS (EI^+) calcd. for $C_{13}H_8NClO$ $[M]^+$ 229.0294, found 229.0305.

5-Phenyl-1*H*-benzo-1,4-diazepin-2(3*H*)-one (10a): According to the general procedure for the aza-Wittig reaction, **9a** (37 mg, 0.16 mmol) was converted into 5-phenyl-1*H*-benzo-1,4-diazepin-2(3*H*)-one (37 mg, 88%) and isolated by column chromatography (5→20% EtOAc in heptane) as a yellow solid. IR (neat): $\tilde{\nu}$ = 1679, 1607, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.55 (s, 1 H), 7.62 7.50 (m, 3 H), 7.50 7.44 (m, 1 H), 7.43 7.37 (m, 2 H), 7.34 (dd, J = 7.9, 1.4 Hz, 1 H), 7.22 (dd, J = 8.1, 0.8 Hz, 1 H), 7.17 (td, J = 8.0, 1.1 Hz, 1 H), 4.36 (s, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.25, 171.10, 139.46, 138.80, 131.70, 131.37, 130.29, 129.69, 128.17, 127.27, 123.33, 121.16, 56.69 ppm. HRMS (ESI^+) calcd. for $C_{15}H_{13}N_2O$ $[M + H]^+$: 237.1028, found 237.1028.

5-Methoxy-1-methyl-1*H*-benzo-1,4-diazepin-2(3*H*)-one (10c): According to the general procedure for the aza-Wittig reaction, **9c** (27 mg, 0.13 mmol) was converted into 5-methoxy-1-methyl-1*H*-benzo-1,4-diazepin-2(3*H*)-one (27 mg, 66%) as isolated by column chromatography (0→10% EtOAc in heptane) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1675, 1322, 1276, 772 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (ddd, J = 7.6, 1.6, 0.6 Hz, 1 H), 7.55 (ddd, J = 8.3, 7.4, 1.7 Hz, 1 H), 7.28–7.24 (m, 2 H), 4.32 (br. s, 1 H), 3.90 (s, 3 H), 3.66 (br. s, 1 H), 3.39 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.10, 163.97, 142.76, 131.71, 128.45, 124.61, 124.48, 120.90, 54.10, 52.38, 34.99 ppm. HRMS (ESI^+) calcd. for $C_{11}H_{13}N_2O_2$ $[M + H]^+$ 205.0977, found 205.0972.

***N*-(2-Aminobenzoyl)-α-methylalanine Methyl Ester (13b):** According to the general procedure for the aza-Wittig reaction, from the reaction of *N*-(2-azidobenzoyl)-α-methylalanine methyl ester (**11d**, 100 mg, 0.381 mmol), *N*-(2-amino-benzoyl)-α-methylalanine methyl ester (52 mg, 58%) was obtained as a yellow oil. IR (neat): $\tilde{\nu}$ = 3464, 3343, 2984, 2946, 1718, 1636, 1515, 1148, 746 cm^{-1}. Mixture of rotamers: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, J = 4.9, 3.6 Hz, 1 H), 7.19 (ddd, J = 8.2, 7.3, 1.5 Hz, 1 H), 6.70–6.52 (m, 3 H), 5.52 (br. s, 2 H), 3.75 (d, J = 1.9 Hz, 3 H), 1.64 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.74, 168.28, 148.30, 131.90, 126.87, 116.79, 116.03, 115.34, 76.95, 76.72, 76.52, 76.10, 56.01, 52.15, 24.50 ppm. HRMS (ESI^+) calcd. for $C_{12}H_{17}N_2O_3$ $[M + H]^+$ 237.1239, found 237.1251.

2-Methoxy-4-methyl-3*H*-benzo-1,4-diazepin-5(4*H*)-one (12c): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)sarcosine methyl ester (**11b**, 150 mg, 604 μmol) was converted into **12b** (28 mg, 23%) which was obtained as a colorless solid. IR (neat): $\tilde{\nu}$ = 2924, 2358, 1653, 1260, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (ddd, J = 7.9, 1.7, 0.5 Hz, 1 H), 7.43 (ddd, J = 8.0, 7.3, 1.7 Hz, 1 H), 7.23–7.12 (m, 2 H), 3.90 (s, 3 H), 3.74 (s, 2 H), 3.22 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.04, 162.98, 144.88, 131.72, 130.88, 127.58, 126.19, 124.52, 54.62, 48.55, 36.50 ppm. HRMS (ESI^+) calcd. for $C_{11}H_{13}N_2O_2$ $[M + H]^+$ 205.0977, found 205.0978.

4-Benzyl-2-methoxy-3*H*-benzo-1,4-diazepin-5(4*H*)-one (12d): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)-*N*-benzylglycine methyl ester (**11c**, 150 mg, 0.462 mmol) was converted to **12c** (14 mg, 11%) which was isolated as a colorless oil; **13d** (66 mg, 48%) was obtained as a white solid. IR (neat): $\tilde{\nu}$ = 1632, 1597, 1446, 1260, 776, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.08–8.02 (m, 1 H), 7.49 (ddd, J = 8.0, 7.3, 1.7 Hz, 1 H), 7.40–7.31 (m, 5 H), 7.26 (ddd, J = 7.9, 7.3, 1.3 Hz, 1 H), 7.18 (dd, J = 8.0, 0.9 Hz, 1 H), 4.87 (s, 2 H), 3.78 (s, 3 H), 3.71 (s, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.94, 163.24, 144.94, 136.66, 131.78, 131.02, 128.69, 128.18, 127.73, 127.37, 126.17, 124.46, 54.29, 51.76, 46.03 ppm. HRMS (ESI^+) calcd. for $C_{17}H_{17}N_2O_2$ $[M + H]^+$ 281.1290, found 281.1289.

***N*-(2-Aminobenzoyl)-*N*-benzylglycine Methyl Ester (13d):** IR (neat): $\tilde{\nu}$ = 3218, 1688, 1627, 1476, 1143, 754, 724, 694 cm^{-1}. Mixture of rotamers: ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (dd, J = 7.9, 1.5 Hz, 1 H), 7.70 (s, 1 H), 7.54–7.44 (m, 1 H), 7.41–7.28 (m, 6 H), 6.94 (dd, J = 8.0, 0.8 Hz, 1 H), 4.88 (s, 2 H), 3.82 (s, 2 H), 3.49 (d, J = 5.3 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.85,

167.24, 136.16, 135.58, 132.62, 132.10, 128.84, 128.35, 127.98, 126.49, 125.39, 120.44, 51.91, 50.91, 49.87 ppm. HRMS (ESI^+) calcd. for $C_{17}H_{19}N_2O_3$ $[M + H]^+$ 299.1396, found 299.1401.

Note: In the ^1H NMR spectrum the peak at δ = 3.49 ppm has a relative integration of 1.19H. However, the HSQC and DEPT135 spectra verify that this peak is attributable to the methyl ester. This effect is probably caused by rotamers although temperature variations from 298 K up to 323 K failed to significantly change the integration of this signal.

(*S*)-3,4-Dibenzyl-2-methoxy-3*H*-benzo-1,4-diazepin-5(4*H*)-one (12e): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)-*N*-benzylphenylalanine methyl ester (**11e**, 150 mg, 0.362 mmol) was converted into **12e** (14 mg, 10%) which was isolated as a yellow oil. Additionally, 53% of the starting material was recovered. IR (neat): $\tilde{\nu}$ = 3023, 1662, 1632, 1450, 767, 711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (ddd, J = 7.9, 1.6, 0.4 Hz, 1 H), 7.69–7.44 (m, 1 H), 7.42–7.04 (m, 10 H), 6.88–6.69 (m, 2 H), 4.94 (d, J = 14.6 Hz, 1 H), 4.27 (d, J = 14.6 Hz, 1 H), 4.08 (dd, J = 9.0, 8.1 Hz, 1 H), 3.58 (s, 3 H), 2.48 (ddd, J = 21.5, 13.4, 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.43, 162.71, 142.87, 136.21, 135.62, 133.84, 131.68, 130.58, 128.27, 128.11, 127.97, 127.24, 126.86, 126.53, 125.64, 124.12, 61.11, 53.54, 53.09, 34.06 ppm. HRMS (ESI^+) calcd. for $C_{24}H_{23}N_2O_2$ $[M + H]^+$ 371.1760, found 371.1958.

(*S*)-11-Methoxy-2,3-dihydro-1*H*-benzopyrrolo[1,2-*a*][1,4]diazepin-5(11a*H*)-one (12f): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)-L-proline methyl ester (**11f**, 27.1 mg, 0.099 mmol) was converted into **12f** (20 mg, 81%) which was isolated as a yellow oil. IR (neat): $\tilde{\nu}$ = 2941, 1649, 1627, 1450, 1407, 1312 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.95 (m, 1 H), 7.45 (ddd, J = 8.0, 7.3, 1.6 Hz, 1 H), 7.23–7.14 (m, 2 H), 4.02–3.97 (m, 1 H), 3.90 (s, 3 H), 3.87 (dd, J = 7.6, 7.1 Hz, 1 H), 3.57–3.50 (m, 1 H), 2.62 (ddd, J = 6.2, 3.7, 2.4 Hz, 1 H), 2.06–2.00 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.95, 162.49, 144.29, 131.72, 130.33, 127.54, 126.56, 124.29, 54.71, 54.61, 46.98, 26.72, 24.12 ppm. HRMS (ESI^+) calcd. for $C_{13}H_{15}N_2O_2$ $[M + H]^+$ 231.1134, found 231.1135.

(2*R*,11a*S*)-2-Hydroxy-11-methoxy-2,3-dihydro-1*H*-benzopyrrolo-[1,2-*a*][1,4]diazepin-5(11a*H*)-one (12g): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)-L-4-*trans*-hydroxyproline methyl ester (**11g**, 150 mg, 0.517 mmol) was converted into **12g** (81 mg, 64%) which was isolated as a yellow oil. IR (neat): $\tilde{\nu}$ = 3352, 2946, 1662, 1614, 1459, 1316, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.79 (m, 1 H), 7.46–7.39 (m, 1 H), 7.18–7.07 (m, 2 H), 4.61–4.50 (m, 1 H), 4.15 (dt, J = 11.4, 5.7 Hz, 1 H), 3.88 (s, 3 H), 3.80 (ddd, J = 12.6, 3.4, 1.4 Hz, 1 H), 3.69 (dd, J = 12.6, 4.7 Hz, 1 H), 3.53 (br. s, 1 H), 2.75 (ddd, J = 13.5, 6.2, 5.3 Hz, 1 H), 2.13 (dddd, J = 13.6, 8.0, 4.3, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.84, 161.78, 144.30, 131.91, 130.34, 126.62, 126.42, 124.41, 68.91, 54.90, 54.55, 53.67, 34.76 ppm. HRMS (ESI^+) calcd. for $C_{13}H_{15}N_2O_3$ $[M + H]^+$ 247.1083, found 247.1087.

6-Methoxy-7,8,9,10-tetrahydrobenzo[*e*]pyrido[1,2-*a*][1,4]diazepin-12(6a*H*)-one (12h): According to the general procedure for the aza-Wittig reaction, *N*-(2-azidobenzoyl)-pipecolinic methyl ester (**11h**, 750 mg, 2.60 mmol) was converted into **12h** (46 mg, 7%) and isolated as a yellow oil; **13h** (619 mg, 91%) was also isolated as a yellow oil. IR (neat): $\tilde{\nu}$ = 2941, 2859, 1640, 1450, 1333, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (ddd, J = 7.8, 1.6, 0.4 Hz, 1 H), 7.42 (ddd, J = 8.0, 7.3, 1.7 Hz, 1 H), 7.15 (dddd, J = 8.0, 4.3, 1.7, 0.9 Hz, 2 H), 4.50–4.39 (m, 1 H), 4.07 (dd, J = 6.6, 3.2 Hz, 1 H), 3.91 (s, 3 H), 2.95 (ddd, J = 13.7, 12.2, 3.8 Hz, 1 H), 2.22–2.08 (m, 1 H), 1.92–1.47 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.17, 164.79, 144.62, 131.52, 130.43, 128.32, 125.76, 124.41, 54.39, 49.50, 40.12, 23.33, 23.03, 19.68 ppm. HRMS (ESI^+) calcd. for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1290, found 245.1295.

***N*-(2-Aminobenzoyl)-pipecolinic Methyl Ester (13h):** IR (neat): $\tilde{\nu}$ = 3443, 3360, 2937, 2683, 1731, 1614, 1420, 1217, 1001, 746 cm^{-1}. Mixture of rotamers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.08 (m, 2 H), 6.82–6.60 (m, 2 H), 5.56 (br. s, 1 H), 4.43–4.25 (br. s, 2 H), 3.78 (s, 3 H), 3.73–3.61 (m, 1 H), 3.40–3.09 (m, 1 H), 2.51–2.20 (m, 1 H), 1.91–1.07 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.07, 171.10, 144.73, 130.68, 127.77, 120.26, 117.67, 116.16, 52.61, 52.29, 45.11, 26.69, 25.53, 21.46 ppm. HRMS (ESI^+) calcd. for $C_{14}H_{19}N_2O_3$ $[M + H]^+$ 263.1396, found 263.1402.

(*S*)-7-Chloro-11-methoxy-2,3-dihydro-1*H*-benzopyrrolo[1,2-*a*][1,4]-diazepin-5(11a*H*)-one (12i): According to the general procedure for the aza-Wittig reaction, *N*-(2-azido-5-chlorobenzoyl)-L-proline methyl ester (150 mg, 0.486 mmol) was converted into **12i** (27 mg, 21%) which was isolated as a yellow solid; **13i** (65 mg, 54%) was isolated as a white solid. IR (neat): $\tilde{\nu}$ = 2950, 2358, 1649, 1437, 1308, 1118, 1091, 996, 832, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.94 (m, 1 H), 7.39 (dd, J = 8.6, 2.6 Hz, 1 H), 7.16–7.08 (m, 1 H), 3.97 (dd, J = 7.7, 1.8 Hz, 1 H), 3.89 (s, 3 H), 3.89–3.82 (m, 1 H), 3.57–3.46 (m, 1 H), 2.67–2.60 (m, 1 H), 2.12–1.98 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.03, 162.04, 142.23, 131.15, 129.29, 129.13, 128.11, 127.59, 54.24, 54.00, 46.49, 26.08, 23.41 ppm. HRMS (ESI^+) calcd. for $C_{13}H_{14}ClN_2O_2$ $[M + H]^+$ 265.0744, found 265.0745.

(*S*)-7-Chloro-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (13i): IR (neat): $\tilde{\nu}$ = 3239, 2950, 2358, 1701, 1627, 1480, 1437, 819, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 7.98 (d, J = 2.5 Hz, 1 H), 7.43 (dd, J = 8.6, 2.5 Hz, 1 H), 6.95 (d, J = 8.6 Hz, 1 H), 4.07 (dd, J = 7.6, 1.7 Hz, 1 H), 3.91–3.73 (m, 1 H), 3.67–3.54 (m, 1 H), 2.82–2.74 (m, 1 H), 2.15–1.95 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.20, 163.54, 133.14, 132.00, 130.43, 130.34, 127.99, 121.89, 56.16, 46.99, 25.80, 22.96 ppm. HRMS (ESI^+) calcd. for $C_{12}H_{12}ClN_2O_2$ $[M + H]^+$ 251.0587, found 251.0583.

Methyl 2-Methoxy-4-methyl-1*H*-pyrrole-3-carboxylate (16): According to the general procedure for the aza-Wittig reaction, dimethyl 2-(1-azidopropan-2-ylidene)malonate (**14**) (53 mg, 0.235 mmol) was converted into **17** (26 mg, 65% yield) which was obtained as an off-white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 6.05 (td, J = 2.2, 1.1 Hz, 1 H), 3.96 (s, 3 H), 3.81 (s, 3 H), 2.20 (d, J = 1.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.80, 150.67, 119.46, 107.12, 96.37, 60.22, 50.07, 12.51 ppm.

Data in correspondence with that in literature.[15]

Supporting Information (see footnote on the first page of this article): See the Supporting Information for the synthetic procedures, ^1H and ^{13} NMR spectra of all compounds.

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