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One-Pot Reductive 1,3-Dipolar Cycloaddition of Secondary Amides: A Two-Step Transformation of Primary Amides

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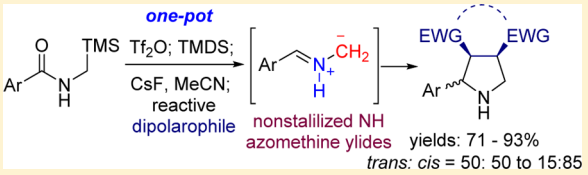
Supporting Information

ABSTRACT: The one-pot reductive 1,3-dipolar cycloaddition of secondary aromatic *N*-(trimethylsilylmethyl)amides with reactive dipolarophiles is reported. The method relies on the in situ generation of nonstabilized NH azomethine ylide dipoles via amide activation with triflic anhydride, partial reduction with 1,1,3,3-tetramethyldisiloxane (TMDS), and desilylation with cesium fluoride (CsF). Running under mild conditions, the reaction tolerated several sensitive functional groups and provided cycloadducts in 71−93% yields. The use of less reactive dipolarophile methyl acrylate led to the cycloadduct in only 40% yield. A (*Z*) geometric intermediate of NH-azomethine 1,3-dipole was postulated to account for the observed higher yields and higher *cis* diastereoselectivity for the substrates bearing an electron-withdrawing group. This model features an unconventional cyclic transition state via carbanion−aryl ring interaction. Because the starting secondary amides can be prepared from common primary amides, the current method also constitutes a two-step transformation of primary amides.

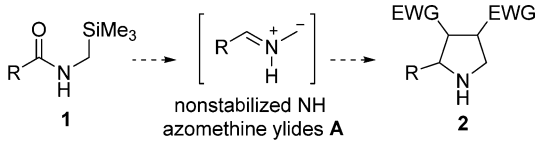


INTRODUCTION

The direct transformation of amides to other classes of compounds has attracted considerable attention in recent years.[1−4] However, in contrast to the many methods developed for the transformation of common tertiary[3] and secondary amides,[4] the direct transformation of primary amides involving C−C bond formation is rare.[5] To the best of our knowledge, only the reductive alkylation of primary amides has been reported, which involves the one-pot dehydration of benzamides with organocerium reagents to benzonitriles and subsequent nucleophilic addition to give tertiary carbinamines.[5]

Azomethine-based 1,3-dipolar cycloaddition is a powerful methodology for the synthesis of substituted pyrrolidines, pyrrolizidines, and related alkaloids.[6] Among the many aspects of this chemistry, the generation and cycloaddition of nonstabilized azomethines occupies a special position. Indeed, at the early phase of its development, Vedejs and co-workers demonstrated in 1980 that tertiary *N*-(silylmethyl)lactams could serve as precursors of nonstabilized azomethine ylides, namely, imidate methylides.[7a] The method consists of *O*-methylation of the amide carbonyl followed by desilylation with CsF. Subsequent investigation showed that an improved yield could be obtained by using thioamides to replace amides.[7b,c] Since this seminal work, several research groups including those of Livinghouse,[8] Padwa,[9] and Snieckus[10] have contributed to the chemistry of tertiary amide-based 1,3-dipolar cycloaddition reactions. Very recently, Chida and Sato have developed an elegant one-pot catalytic reductive transformation of tertiary *N*-hydroxyamides to nitrones followed by 1,3-dipolar cycloaddition.[11] However, the secondary amide-based reductive 1,3-dipolar cycloaddition reaction that involves the generation of the singular nonstabilized *N*-protonated (NH) azomethine ylides **A** (Scheme 1) is elusive.[12,13]

Scheme 1. Envisioned Generation and Cycloaddition of Nonstabilized NH Azomethine Ylides A from Secondary Amides



In this regard, the thermal 1,4-silatropic generation of azomethine ylides **B-1** and **B-2** from methyl *N*-(disilylmethyl)/*N*-(phenylsilylmethyl)benzimidate **3a**/**b** and *N*-(phenylsilylmethyl)benzamide **4** developed by Komatsu and co-workers remains the sole secondary amide-based 1,3-dipolar cycloaddition.[12] After a workup procedure, desilylated product **5a** was isolated, which allowed viewing the azomethine ylide **B-1** as a synthetic equivalent of α-nonsubstituted analogue **C** and nitrile ylide **D** (Scheme 2).[12c] However, this method requires an ylide-stabilizing group such as Ph or Me_3Si at the α-carbon. For a stabilizing group-free method to be developed, *N*-(stannylmethyl)thioamide **6** was introduced for the one-pot thermal 1,4-stannatropy and 1,3-dipolar cycloaddition.[12d] Nevertheless, although **7** could be obtained in 31−96% yields,

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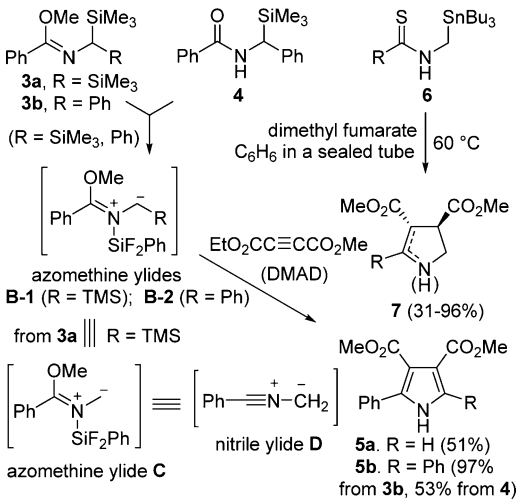
Scheme 2. Komatsu's 1,4-Sila- and Stannatropic Strategies for the Generation and Cycloaddition of 1,3-Dipoles



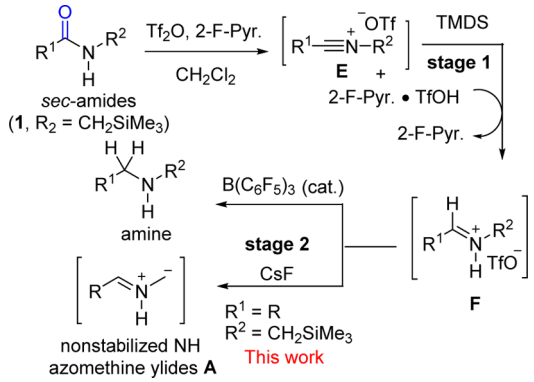
this method requires an additional step to prepare thioamide **6** from the corresponding amide. Thus, direct generation and reaction of nonstabilized NH azomethine ylides of type **A** from secondary amides remain challenging.[12d]

Very recently, we have developed several methods for the direct transformation of secondary amides, which include reductive alkylation,[14a] reductive coupling with ketones,[14b] reductive Ugi-type reaction,[14c] aza-Knoevenagel-type condensation,[14d] and reductive cycloaddition with Danishefsky diene.[14e] In connection with those studies, we report herein the Tf_2O-mediated direct reductive 1,3-dipolar cycloaddition of secondary *N*-(trimethylsilylmethyl)amides **1** (Scheme 1) readily available from acyl chlorides and (trimethylsilyl)-methylamine. We also disclosed that secondary amides **1** can be prepared by trimethylsilylmethylation of primary amides, which established a two-step transformation of common primary amides.

RESULTS AND DISCUSSION

Recently, we have reported the one-pot two-stage catalytic hydrosilylation of secondary amides employing Tf_2O-TMDS-$B(C_6F_5)_3$ (cat.) combination[15] in which triflic anhydride[16] (Tf_2O) was used to activate the amide group and 1,1,3,3-tetramethyldisiloxane (TMDS) served as a partial reducing agent to generate the iminium salt **F**[14,15] (stage 1, Scheme 3). The subsequent $B(C_6F_5)_3$-catalyzed reduction of **F** produced

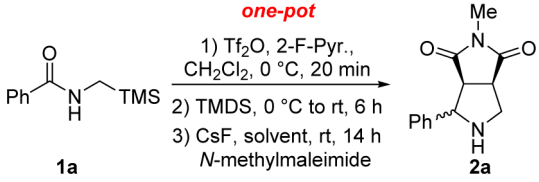
Scheme 3



an amine (stage 2).[15] It was envisaged that by employing *N*-(trimethylsilylmethyl)amide **1** as a starting amide, after the amide activation-partial reduction with Tf_2O-TMDS, the presumed iminium ion intermediate **F** could be used as a ready precursor of the nonstabilized NH azomethine ylide dipole **A**.

We started our investigation by screening the solvent for the reaction. Given that dichloromethane is the solvent of choice for the amide activation and subsequent partial reduction,[14,15] it was selected for the one-pot reductive cycloaddition. In this event, secondary amide **1a** was successively treated with Tf_2O (1.1 equiv), 2-fluoropyridine[17] (2-F-Pyr, 1.2 equiv), TMDS (0.7 equiv), CsF (3.0 equiv), and *N*-methylmaleimide (2.0 equiv), which gave desired cycloadduct **2a** in 15% yield (Table 1, entry 1). The low yield observed was attributed to the low

Table 1. Effect of Solvent on the Reductive Cycloaddition Reaction[a]



entry	solvent	yield[b] (%) (*trans*:*cis*)[c]
1	DCM[d]	15 (55:45)
2	DCM[e]	31 (55:45)
3	THF[e]	69 (52:48)
4	1,4-dioxane[e]	65 (55:45)
5	DMF[e]	80 (49:51)
6	**MeCN**[e]	**85 (48:52)**
7	DCM[c]/ MeCN[e]	74 (48:52)

[a]Conditions: Tf_2O (1.1 equiv), 2-F-Pyr (1.2 equiv), TMDS (0.7 equiv), CsF (3.0 equiv), and *N*-methylmaleimide (2.0 equiv). [b]Isolated yield. [c]Ratio determined by ^1H NMR of the crude product. [d]Without changing solvent. [e]After the partial reduction, the reaction mixture was concentrated, and a new solvent was added.

efficiency of the desilylation reaction with CsF because, from the ^1H NMR spectrum of the crude product, a signal of aldehyde resulting from the hydrolysis of the iminium ion intermediate **F** was observed. It is possible that the excess TMDS consumed some CsF. For this possibility to be eliminated, after the stage 1, the reaction mixture was concentrated under reduced pressure before addition of a solvent, CsF, and a dipolarophile. Indeed, even using the same CH_2Cl_2 as solvent for the second stage, desired cycloaddition product **2a** was obtained in 31% yield as a 55:45 diastereomeric mixture (Table 1, entry 2). It was further envisioned that the yield of the 1,3-dipolar cycloaddition could be improved by using a polar solvent. To our delight, when polar solvents such as THF, dioxane, and DMF were used, the yield of **2a** was improved to 69, 65, and 80%, respectively (entries 3−5). The best yield (85%) was obtained with the use of acetonitrile as a convenient polar solvent (entry 6). Thus, the conditions outlined in entry 6 were used in the subsequent investigation for the higher yield. Alternatively, an operationally simpler protocol alleviating the change of solvent was also established, which employed CH_2Cl_2/MeCN as a mixed solvent system and afforded cycloadduct **2a** in 74% yield (entry 7). It is worth noting that the order of efficiencies of solvents observed in this investigation is different from that observed for a related

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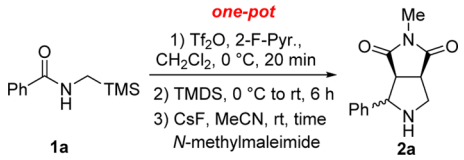
trimethylsilyl triflate-catalyzed 1,3-dipolar cycloaddition in which the following order has been observed: DMF ≫ DME > THF ≫ acetonitrile > dichloromethane.[18]

Next, other reaction parameters including reaction time (Table 2, entries 1−3), equiv of dipolarophile (entries 4 and 5),

Table 2. Further optimization of the reaction conditions



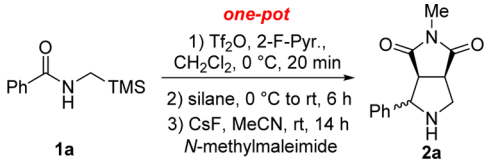
entry	time (h)	dipolarophile (*n* equiv)	CsF (*n* equiv)	yield[a] (%) (*trans*:*cis*)[b]
1	14	2.0	3.0	85 (48:52)
2	7	2.0	3.0	62 (48:52)
3	20	2.0	3.0	85 (48:52)
4	14	1.5	3.0	76 (48:52)
5	14	2.5	3.0	85 (48:52)
6	14	2.0	2.0	63 (48:52)
7	**14**	**2.0**	**4.0**	**91 (48:52)**
8	14	2.0	5.0	88 (48:52)

[a]Isolated yield. [b]Determined by ^{1}H NMR of the crude product.

and CsF (entries 6−8) were examined, which allowed for determining the optimized reaction conditions as those shown in entry 7 (Table 2).

Finally, several silanes including TMDS, PMHS, $(EtO)_3SiH$, Et_3SiH, $i\text{-}Pr_3SiH$, $PhMe_2SiH$, and $PhSiH_3$ were examined as the reducing reagents (Table 3) from which TMDS (entry 1) turned out to be the best, producing **2a** in 91% yield.

Table 3. Screening of Silanes[a]

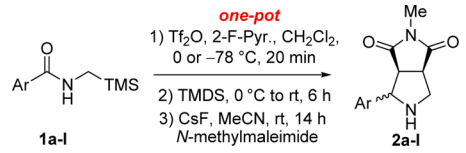


entry	silane (*n* equiv)	yield[b] (%) (*trans*:*cis*)[c]
1	**TMDS (0.7)**	**91 (48:52)**
2	PMHS (1.4 Si−H)	51 (47:53)
3	$(EtO)_3SiH$ (1.4)	18 (48:52)
4	Et_3SiH (1.4)	87 (48:52)
5	$i\text{-}Pr_3SiH$ (1.4)	84 (48:52)
6	$PhMe_2SiH$ (1.4)	86 (48:52)
7	$PhSiH_3$ (1.4)	74 (48:52)

[a]Conditions: Tf_2O (1.1 equiv), 2-F-Pyr (1.2 equiv), silane (1.4 equiv Si−H), CsF (4.0 equiv), and *N*-methylmaleimide (2.0 equiv). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude product.

After defining the optimal reaction conditions for the direct reductive 1,3-dipolar cycloaddition of *N*-(trimethylsilylmethyl)-amide **1a** with *N*-methylmaleimide, we turned our attention to exploring the scope of the reaction. A series of secondary amides **1b−l** were examined, and the results are displayed in Table 4. *Para*-, *meta*-, and *ortho*-methylbenzamides produced the corresponding adducts in 83 (**2b**), 81 (**2c**), and 78% (**2d**) yield, respectively (entries 2−4). Introduction of an electron-donating group (Me, OMe, entries 2 and 3) onto the para position of the benzene ring of benzamide led to a decrease in

Table 4. Reductive 1,3-Dipolar Cycloaddition of *N*-(Silylmethyl)amides 1a−l with *N*-Methylmaleimide



entry	substrate (Ar)		yield (%)[a] (*trans*:*cis*)[b]
1	**1a**	Ph	91[c] (48:52)
2	**1b**	*p*-MeC_6H_4	83[c] (40:60)
3	**1c**	*m*-MeC_6H_4	81[c] (41:59)
4	**1d**	*o*-MeC_6H_4	78[c] (48:52)
5	**1e**	*p*-$MeOC_6H_4$	71[c] (45:55)
6	**1f**	*p*-$CF_3C_6H_4$	91[c] (38:62)
7	**1g**	*p*-BrC_6H_4	90[c] (32:68)
8	**1h**	*p*-NCC_6H_4	93[d] (31:69)
9	**1i**	*p*-$AcOC_6H_4$	88[d] (46:54)
10	**1j**	*p*-$MeO_2CC_6H_4$	86[d] (37:63)
11	**1k**	*p*-$O_2NC_6H_4$	61[c]/89[d] (15:85)[c,d]
12	**1l**	2-Thienyl	85[c] (47:53)

[a]Isolated yield. [b]Ratio determined by ^{1}H NMR of the crude product and stereochemistry determined by correlating with **2a**. [c]Activation of the amide performed at 0 °C for 20 min, then reduction with TMDS performed at 0 °C for 0.5 h and at rt for 5 h. [d]Activation of the amide performed at −78 °C for 20 min and then at 0 °C for 5 min, then reduction with TMDS performed at 0 °C for 3 h and at rt for 4 h.

yield (**2b**: 83%, **2e**: 71 versus 91% for benzamide **2a**, entry 1). Benzamide derivatives bearing electron-withdrawing groups such as CF_3 and Br afforded cycloadducts **2f** and **2g** in high yields (91 and 90%, entries 6 and 7). As can be seen from entries 8−11, when performing the amide activation step at −78 °C, the reaction tolerates sensitive functional groups such as cyano (**1h**), ester [OAc (**1i**), CO_2Me (**1j**)], and nitro (**1k**) groups, and the reaction took place chemoselectively at the secondary amide group. Note that when the amide activation was performed at rt, the yield of **2k** was only 61% (entry 11). *N*-Isopropyl-thiophene-2-carboxamide **1l**, a heteroaromatic amide, also reacted smoothly to give desired adduct **2l** in 85% yield (entry 12). The trans/cis stereochemistries were assigned on the basis of the observed chemical shifts of H-2 in the cycloadducts ($\delta_{trans} > \delta_{cis}$) and coupling constants (J_{trans} = 0−2.5 Hz, J_{cis} = 7.6−8.1 Hz).[13a,b]

For the nonstabilized NH azomethine ylide **G** (X = H, Figure 1) to be probed, triethylamine was introduced before the

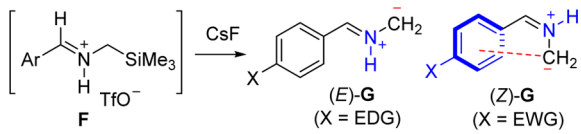


Figure 1. Plausible substituent-dependent geometric isomers of the nonstabilized NH azomethine ylide dipoles **G**.

addition of a dipolarophile. When 1.5 equiv of triethylamine was introduced, the yield of cycloadduct **2a** dropped to 41%, whereas with 3.0 equiv of triethylamine, less than 5% of **2a** was observed. These results allow for assuming the intermediacy of the NH azomethine ylide **G**.

The cycloaddition reactions showed poor diastereoselectivities. This phenomenon is generally observed[12,13] for the 1,3-dipolar cycloaddition reactions of nonstabilized NH azome-

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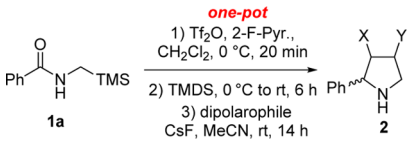
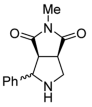
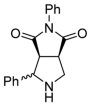
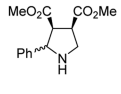
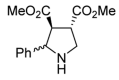
thine ylides bearing no α-chelating group.[19] However, the higher yields and higher diastereoselectivities (approximately 2:1 to 5:1) observed for the benzamides bearing electron-withdrawing groups on the benzene ring (Table 4, entries 6–11) as compared with those bearing electron-donating groups (Table 4, entries 2–5) is unusual. This is because the cycloaddition such as that displayed in Scheme 1 is believe to be controlled by the HOMO (dipole)–LUMO (dipolarophile) interaction, which should be accelerated by electron-donating substituents in the dipole.[6c] On the other hand, (*E*)-NH-azomethine 1,3-dipole [(*E*)-**G**] has been assumed by Tsuge as the major geometric isomer for the related 1,3-dipolar cycloaddition.[13b] To account for the results obtained in this study, we postulate (*Z*)-**G** as the predominant geometric isomer of the NH-azomethine 1,3-dipole bearing an electron-withdrawing group. This model features an unconventional cyclic transition state (*Z*)-**G** via carbanion–aryl ring interaction.[20] On the basis of this model, an electron-withdrawing group enhances the carbanion–aryl ring interaction and thus stabilizes the azomethine ylide (*Z*)-**G**. The corresponding 1,3-dipolar cycloaddition reaction thus affords a higher yield. Moreover, the carbanion–aryl ring interaction leads (*Z*)-**G** to adopt a nonplanar structure, which disfavors a secondary orbital interaction with an incoming dipolarophile. This can account for the observed slightly preferred exo approach to give *cis*-**2** as the major diastereomer. On the other hand, an electron-donating group on the benzene ring of a 1,3-dipole disfavors the carbanion–aryl ring interaction in (*Z*)-**G**, and (*E*)-**G** might be the reactive intermediate, which produces the corresponding cycloadduct in a lower yield and in an almost stereorandom manner.

We next examined the reductive 1,3-dipolar cycloaddition reactions of amide **1a** with different dipolarophiles (Table 5). The reductive cycloaddition with *N*-phenylmaleimide produced **2m** in 90% yield and in 48:52 dr, which are similar to those obtained from the *N*-methyl analogue (91% yield, 48:52 dr).

Table 5. Reductive 1,3-Dipolar Cycloaddition of *N*-(Silylmethyl)amide 1a with Different Dipolarophiles[a]



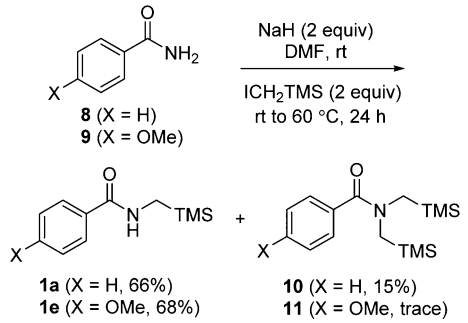
Product (yield[b], *trans*: *cis*[c])		
		
2a (91%, 48: 52)	**2m** (90%, 48: 52)	**2n** (71%, 50: 50)
		
2o (73%, 50: 50)	**2p** (83%, 50: 50)	**2q** (40%, 14: 86)

[a]Conditions: Tf_2O (1.1 equiv), 2-F-Pyr (1.2 equiv), TMDS (0.7 equiv), CsF (4.0 equiv), and *N*-methylmaleimide (2.0 equiv). [b]Isolated yield. [c]Ratio determined by ^1H NMR of crude product, and stereochemistry determined by correlating with the known compound.

Dimethyl maleate, dimethyl fumarate, and fumaronitrile are also suitable dipolarophiles for the reductive cycloaddition, although moderate yields (**2n**, 71%; **2o**, 73%; **2p**, 83%) were obtained. The reaction of amide **1a** with less reactive dipolarophile methyl acrylate produced cycloadduct **2q** in moderate yield (40%).

To further extend the scope of the method, we investigated the preparation of secondary amides **1** from primary amides. Thus, successive treatment of benzamide **8** with NaH (2.0 equiv) and iodomethyltrimethylsilane (2.0 equiv, rt to 60 °C) produced secondary amide **1a** in 66% yield along with tertiary amide **10** in 15% yield and 16% of the recovered starting material (Scheme 4). Similarly, the trimethylsilylmethylation of primary amide **9** afforded secondary amide **1e** in 68% yield along with 16% of the recovered starting material.

Scheme 4



CONCLUSIONS

In summary, we have developed the first direct reductive 1,3-dipolar cycloaddition reaction of secondary amides **1** with reactive dipolarophiles. The reaction conditions are mild, which tolerate several sensitive functional groups including bromo, cyano, acetoxy, ester, and nitro groups. A controlled experiment allowed for confirming the intermediacy of a nonstabilized NH azomethine ylide dipole in the cycloaddition reaction. To the best of our knowledge, the direct generation of a nonstabilized NH azomethine ylide from a secondary amide is unprecedented. Because *N*-(trimethylsilylmethyl)amide substrates are available from primary amides in one step, this method also constitutes a two-step transformation of primary amides involving C–C bond formation, which is rare in the chemistry of amides.

EXPERIMENTAL SECTION

For general experimental methods, see ref 14a. Note: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on an instrument at 500 and 125 MHz, respectively.

General Procedure for the Preparation of *N*-(Trimethylsilylmethyl)amides (General Procedure A). To a dry round-bottom flask equipped with a stirring bar and under argon were successively added (trimethylsilyl)methylamine (1.1 equiv), triethylamine (1.1 equiv), and dichloromethane (0.4 M). The solution was cooled to 0 °C, and acyl chloride (1.0 equiv) was slowly added via a syringe (in the case when an acyl chloride is solid, a solution in dichloromethane was added). Then, the reaction was slowly warmed to rt and stirred overnight. The reaction was diluted with dichloromethane and washed successively with 1 M HCl, brine, a saturated aqueous $NaHCO_3$ solution, and brine and then dried over anhydrous sodium sulfate (Na_2SO_4). The organic layer was filtered and evaporated to dryness to give the crude amide. The crude amide was purified by recrystallization from a mixture of EtOAc/hexane to

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afford pure amide. (Note: Following general procedure A, *N*-(trimethylsilylmethyl)amides **1b**–**l** were prepared at 5.0 mmol scale except for amide **1a**, which was at 50.0 mmol scale.)

General Procedure for the Preparation of *N*-(Trimethylsilylmethyl)amides from Primary Amides (General Procedure B). The solution of primary amide (3.0 mmol) in DMF (5 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.24 g, 6.0 mmol) in dry DMF (15 mL) at rt with efficient stirring under an Ar atmosphere. After 2 h at rt, (iodomethyl)trimethylsilane (890 μL, 1.28 g, 6.0 mmol) was added neat. The resulting mixture was allowed to warm to 60 °C and stirred for 24 h. The reaction was quenched with water (1 mL), and most of solvent was removed under reduced pressure. Water (10 mL) was added and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with sodium thiosulfate ($Na_2S_2O_3$) and brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (300–400 mesh) to give the corresponding secondary amide.

General Procedure for One-Pot Reductive 1,3-Dipolar Cycloaddition of Secondary Amides (General Procedure C). Into a dry 5 mL round-bottom flask equipped with a stirring bar were successively added secondary amide **1** (0.5 mmol), 2 mL of anhydrous dichloromethane, and 2-fluoropyridine (52 μL, 0.6 mmol). After being cooled to −78 or 0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (92 μL, 0.55 mmol) was added dropwise via a syringe at 0 °C, and the reaction mixture was stirred for 20 min. To the resulting mixture was added 1,1,3,3-tetramethyldisiloxane (TMDS) (62 μL, 0.35 mmol) dropwise at 0 °C, and the reaction was stirred for 10 min. The mixture was allowed to warm to rt and stirred for 6 h. The solvent was removed through a drying tube charged with anhydrous $CaCl_2$ under reduced pressure. Acetonitrile (2 mL) was added to dissolve the residue, and then a solution of dipolarophile (1.0 mmol) in acetonitrile (1 mL) was added. The resulting mixture was added dropwise to the suspension of cesium fluoride (304 mg, 2.0 mmol) in acetonitrile (2 mL) with vigorous stirring. The reaction mixture was stirred for another 14 h at rt before addition of an appropriate amount of silica gel (100–200 mesh). The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (300–400 mesh) to give corresponding cycloadduct **2**. (Note: the activation of the amides **1h**–**1k** was performed at −78 °C for 20 min and then at 0 °C for 5 min; the partial reduction with TMDS was performed at 0 °C for 3 h and at rt for 4 h.)

*N-[(Trimethylsilyl)methyl]benzamide (**1a**).* Following general procedure A, amide **1a**[21] was obtained as white crystals (9.20 g, yield: 89%). Following general procedure B, the monotrimethylsilylmethylation of primary amide **8** (at 3 mmol scale) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:4), **1a** as a white solid (410 mg, yield: 66%). Mp: 102–103 °C (lit.[21] mp: 99–100 °C). IR (film) ν_{max}: 3351, 3067, 2958, 1626, 1546, 1310, 1247, 890, 835, 695 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.95 (d, J = 5.8 Hz, 2H), 6.12 (br s, 1H), 7.37–7.50 (m, 3H), 7.71–7.76 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.3, 126.7 (2C), 128.5 (2C), 131.0, 135.1, 167.8 ppm. MS (ESI, m/z): 230 $(M + Na)^+$.

*4-Methyl-N-[(trimethylsilyl)methyl]benzamide (**1b**).* Following general procedure A, amide **1b** was obtained as white crystals (1.02 g, yield: 93%). Mp: 123–124 °C. IR (film) ν_{max}: 3345, 2956, 1623, 1549, 1306, 1118, 894, 840, 750 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.38 (s, 3H), 2.94 (d, J = 5.8 Hz, 2H), 6.03 (br s, 1H), 7.18–7.24 (m, 2H), 7.60–7.66 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 21.4, 30.2, 126.7 (2C), 129.1 (2C), 132.2, 141.4, 167.7 ppm. HRMS-ESI calcd for $[C_{12}H_{19}NOSi + Na]^+$ $(M + Na)^+$: 244.1128; found: 244.1134.

*3-Methyl-N-[(trimethylsilyl)methyl]benzamide (**1c**).* Following general procedure A, amide **1c** was obtained as white crystals (1.01 g, yield: 92%). Mp: 86–87 °C. IR (film) ν_{max}: 3371, 2955, 1630, 1582, 1541, 1247, 845, 737 cm^{-1}. ^1H NMR: δ 0.13 (s, 9H), 2.39 (s, 3H), 2.95 (d, J = 5.8 Hz, 2H), 6.04 (br s, 1H), 7.26–7.32 (m, 2H), 7.46–7.52 (m, 1H), 7.54–7.58 (m, 1H). ^{13}C NMR: δ −2.6 (3C), 21.3, 30.3, 123.5, 127.5, 128.3, 131.8, 135.1, 138.4, 167.9 ppm. HRMS-ESI calcd for $[C_{12}H_{19}NOSi + Na]^+$ $(M + Na)^+$: 244.1128; found: 244.1129.

*2-Methyl-N-[(trimethylsilyl)methyl]benzamide (**1d**).* Following general procedure A, amide **1d** was obtained as white crystals (1.06 g, yield: 96%). Mp: 75–76 °C. IR (film) ν_{max}: 3268, 2954, 1633, 1538, 1319, 1248, 898, 842, 729 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.43 (s, 3H), 2.95 (d, J = 5.7 Hz, 2H), 5.63 (br s, 1H), 7.15–7.23 (m, 2H), 7.25–7.34 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 19.7, 30.1, 125.7, 126.6, 129.6, 130.9, 135.9, 137.0, 170.2 ppm. HRMS-ESI calcd for $[C_{12}H_{19}NOSi + Na]^+$ $(M + Na)^+$: 244.1128; found: 244.1133.

*4-Methoxy-N-[(trimethylsilyl)methyl]benzamide (**1e**).* Following general procedure A, amide **1e** was obtained as white crystals (1.07 g, yield: 90%). Following general procedure B, the monotrimethylsilylmethylation of primary amide **9** (in 3 mmol scale) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/3), **1e** as a white solid (484 mg, yield: 68%). Mp: 91–92 °C. IR (film) ν_{max}: 3330, 2954, 1621, 1553, 1505, 1250, 842 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.94 (d, J = 5.8 Hz, 2H), 3.83 (s, 3H), 6.25 (br s, 1H), 6.86–6.92 (m, 2H), 7.68–7.75 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.1, 55.2, 113.5 (2C), 127.3, 128.4 (2C), 161.7, 167.2 ppm. HRMS-ESI calcd for $[C_{12}H_{19}NO_2Si + Na]^+$ $(M + Na)^+$: 260.1077; found: 260.1080.

*4-(Trifluoromethyl)-N-[(trimethylsilyl)methyl]benzamide (**1f**).* Following general procedure A, amide **1f** was obtained as white crystals (1.21 g, yield: 88%). Mp: 62–63 °C. IR (film) ν_{max}: 3285, 2957, 1637, 1552, 1327, 1169, 1131, 1069, 857 cm^{-1}. ^1H NMR: δ 0.13 (s, 9H), 2.97 (d, J = 5.7 Hz, 2H), 6.26 (br s, 1H), 7.62–7.69 (m, 2H), 7.80–7.86 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.6, 123.7 (q, J_{F-C} = 272.0 Hz), 125.5 (2C), 127.2 (2C), 132.8 (q, J_{F-C} = 32.5 Hz), 138.4, 166.5 ppm. HRMS-ESI calcd for $[C_{12}H_{16}F_3NOSi + Na]^+$ $(M + Na)^+$: 298.0846; found: 298.0847.

*4-Bromo-N-[(trimethylsilyl)methyl]benzamide (**1g**).* Following general procedure A, amide **1g** was obtained as white crystals (1.37 g, yield: 96%). Mp: 96–97 °C. IR (film) ν_{max}: 3319, 2954, 1623, 1548, 1484, 1249, 839 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.94 (d, J = 5.8 Hz, 2H), 6.05 (br s, 1H), 7.53–7.64 (m, 4H). ^{13}C NMR: δ −2.6 (3C), 30.4, 125.7, 128.3 (2C), 131.7 (2C), 133.9, 166.8 ppm. HRMS-ESI calcd for $[C_{11}H_{16}BrNOSi + Na]^+$ $(M + Na)^+$: 308.0077 and 310.0056; found: 308.0078 and 310.0058.

*4-Cyano-N-[(trimethylsilyl)methyl]benzamide (**1h**).* Following general procedure A, amide **1h** was obtained as white crystals (1.03 g, yield: 89%). Mp: 131–132 °C. IR (film) ν_{max}: 3346, 2965, 2229, 1631, 1548, 1247, 836 cm^{-1}. ^1H NMR: δ 0.13 (s, 9H), 2.97 (d, J = 5.8 Hz, 2H), 6.18 (br s, 1H), 7.68–7.75 (m, 2H), 7.80–7.86 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.7, 114.6, 118.0, 127.5 (2C), 132.3 (2C), 139.0, 165.9 ppm. HRMS-ESI calcd for $[C_{12}H_{16}N_2OSi + Na]^+$ $(M + Na)^+$: 255.0924; found: 255.0928.

*4-{[(Trimethylsilyl)methyl]carbamoyl}phenyl Acetate (**1i**).* Following general procedure A, amide **1i** was obtained as white crystals (1.25 g, yield: 94%). Mp: 94–95 °C. IR (film) ν_{max}: 3307, 2954, 1759, 1633, 1544, 1500, 1199, 843 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.32 (s, 3H), 2.94 (d, J = 5.8 Hz, 2H), 6.35 (br s, 1H), 7.12–7.17 (m, 2H), 7.72–7.78 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 21.0, 30.4, 121.6 (2C), 128.1 (2C), 132.7, 152.6, 166.9, 169.1 ppm. HRMS-ESI calcd for $[C_{13}H_{19}NO_3Si + Na]^+$ $(M + Na)^+$: 288.1026; found: 288.1032.

*Methyl 4-{[(Trimethylsilyl)methyl]carbamoyl}benzoate (**1j**).* Following general procedure A, amide **1j** was obtained as white crystals (1.21 g, yield: 88%). Mp: 100–101 °C. IR (film) ν_{max}: 3292, 2953, 1727, 1635, 1545, 1281, 1108, 843 cm^{-1}. ^1H NMR: δ 0.13 (s, 9H), 2.97 (d, J = 5.8 Hz, 2H), 3.93 (s, 3H), 6.35 (br s, 1H), 7.75–7.80 (m, 2H), 8.03–8.07 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.6, 52.3, 126.8 (2C), 129.7 (2C), 132.2, 139.0, 166.3, 166.8 ppm. HRMS-ESI calcd for $[C_{13}H_{19}NO_3Si + Na]^+$ $(M + Na)^+$: 288.1026; found: 288.1038.

*4-Nitro-N-[(trimethylsilyl)methyl]benzamide (**1k**).* Following general procedure A, amide **1k**[22] was obtained as white crystals (1.20 g, yield: 95%). Mp: 124–125 °C (lit.[22] mp: 123.5–124 °C). IR (film) ν_{max}: 3360, 2964, 1632, 1593, 1519, 1347, 1300, 1246, 1109, 834 cm^{-1}. ^1H NMR: δ 0.14 (s, 9H), 2.99 (d, J = 5.8 Hz, 2H), 6.15 (br s, 1H), 7.87–7.91 (m, 2H), 8.25–8.30 (m, 2H). ^{13}C NMR: δ −2.6 (3C), 30.9, 123.7 (2C), 127.9 (2C), 140.7, 149.2, 165.7 ppm. HRMS-ESI calcd for $[C_{11}H_{16}N_2O_3Si + Na]^+$ $(M + Na)^+$: 275.0822; found: 275.0831.

*N-[(Trimethylsilyl)methyl]thiophene-2-carboxamide (**1l**).* Following general procedure A, amide **1l** was obtained as white crystals (0.98

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g, yield: 85%). Mp: 120−121 °C. IR (film) ν_{max}: 3333, 2959, 1621, 1554, 1310, 1244, 873, 851, 716 cm^{-1}. ^1H NMR: δ 0.12 (s, 9H), 2.93 (d, J = 5.8 Hz, 2H), 5.98 (br s, 1H), 7.05 (t, J = 4.3 Hz, 1H), 7.43 (d, J = 4.9 Hz, 1H), 7.46−7.50 (d, J = 3.6 Hz, 1H). ^{13}C NMR: δ −2.6 (3C), 30.2, 127.5 (2C), 129.2, 139.2, 162.1 ppm. HRMS-ESI calcd for $[C_9H_{15}NOSSi + Na]^+$ $(M + Na)^+$: 236.0536; found: 236.0548.

(3aS,4S*,6aR*)-2-Methyl-4-phenyltetrahydropyrrolo[3,4-c]-pyrrole-1,3(2H,3aH)-dione (trans-**2a**) and (3aS*,4R*,6aR*)-2-Methyl-4-phenyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2a**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1), the known cycloadducts *trans*/*cis*-**2a**[13a] (105 mg, yield: 91%, *trans*:*cis* = 48:52, determined by ^1H NMR of the crude product). *trans*-**2a**: colorless oil. IR (film) ν_{max}: 3327, 2917, 1774, 1697, 1435, 1384, 1282, 737, 701 cm^{-1}. ^1H NMR: δ 1.95 (br s, 1H), 3.03 (s, 3H), 3.33−3.40 (m, 3H), 3.42−3.47 (m, 1H), 4.67 (d, J = 2.5 Hz, 1H), 7.26−7.31 (m, 1H), 7.34−7.41 (m, 4H). ^{13}C NMR: δ 25.2, 46.6, 48.8, 53.1, 64.8, 126.1 (2C), 127.4, 128.7 (2C), 141.3, 178.4, 178.9 ppm. *cis*-**2a**: white solid. Mp: 98−99 °C. IR (film) ν_{max}: 3334, 2926, 2849, 1774, 1699, 1435, 1384, 1284, 1094, 757, 703 cm^{-1}. ^1H NMR: δ 1.86 (br s, 1H), 2.91 (s, 3H), 3.16 (dd, J = 9.7, 7.1 Hz, 1H), 3.28 (t, J = 7.1 Hz, 1H), 3.33 (t, J = 8.1 Hz, 1H), 3.71 (d, J = 9.7 Hz, 1H), 4.39 (d, J = 8.1 Hz, 1H), 7.28−7.38 (m, 5H). ^{13}C NMR: δ 24.9, 45.9, 49.0, 49.3, 65.6, 127.0 (2C), 128.0, 128.3 (2C), 137.7, 175.8, 179.3 ppm. MS (ESI, m/z): 253 $(M + Na)^+$.

(3aS,4S*,6aR*)-2-Methyl-4-(p-tolyl)tetrahydropyrrolo[3,4-c]-pyrrole-1,3(2H,3aH)-dione (trans-**2b**) and (3aS*,4R*,6aR*)-2-Methyl-4-(p-tolyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2b**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1b** (111 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1), cycloadducts *trans*/*cis*-**2b** (101 mg, yield: 83%, *trans*:*cis* = 40:60, determined by ^1H NMR of the crude product). *trans*-**2b**: colorless oil. IR (film) ν_{max}: 3329, 2918, 1774, 1698, 1434, 1384, 1281, 1127, 810 cm^{-1}. ^1H NMR: δ 1.82 (br s, 1H), 2.35 (s, 3H), 3.03 (s, 3H), 3.34−3.38 (m, 3H), 3.40−3.44 (m, 1H), 4.64 (d, J = 1.9 Hz, 1H), 7.10−7.20 (m, 2H), 7.24−7.28 (m, 2H). ^{13}C NMR: δ 21.0, 25.2, 46.6, 48.8, 53.1, 64.7, 126.1 (2C), 129.4 (2C), 137.2, 138.2, 178.4, 179.0 ppm. *cis*-**2b**: white solid. Mp: 148−149 °C. IR (film) ν_{max}: 3335, 2924, 1775, 1699, 1435, 1383, 1316, 1284, 1088, 810 cm^{-1}. ^1H NMR: δ 1.79 (br s, 1H), 2.34 (s, 3H), 2.91 (s, 3H), 3.15 (dd, J = 9.7, 6.9 Hz, 1H), 3.27 (t, J = 6.9 Hz, 1H), 3.31 (t, J = 7.9 Hz, 1H), 3.69 (d, J = 9.7 Hz, 1H), 4.35 (d, J = 7.9 Hz, 1H), 7.12−7.20 (m, 4H). ^{13}C NMR: δ 21.2, 24.9, 46.0, 49.0, 49.3, 65.5, 126.9 (2C), 129.0 (2C), 134.5, 137.6, 175.9, 179.3 ppm. HRMS-ESI calcd for $[C_{14}H_{16}N_2O_2 + Na]^+$ $(M + Na)^+$: 267.1104; found: 267.1103.

(3aS,4S*,6aR*)-2-Methyl-4-(m-tolyl)tetrahydropyrrolo[3,4-c]-pyrrole-1,3(2H,3aH)-dione (trans-**2c**) and (3aS*,4R*,6aR*)-2-Methyl-4-(m-tolyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2c**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1c** (111 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1), cycloadducts *trans*/*cis*-**2c** (99 mg, yield: 81%, *trans*:*cis* = 41:59, determined by ^1H NMR of the crude product). *trans*-**2c**: colorless oil. IR (film) ν_{max}: 3329, 2917, 1775, 1699, 1435, 1383, 1281, 1128, 793 cm^{-1}. ^1H NMR: δ 1.90 (br s, 1H), 2.37 (s, 3H), 3.03 (s, 3H), 3.35−3.40 (m, 3H), 3.43−3.48 (m, 1H), 4.65 (d, J = 2.0 Hz, 1H), 7.08−7.12 (m, 1H), 7.15−7.21 (m, 2H), 7.24−7.28 (m, 1H). ^{13}C NMR: δ 21.5, 25.2, 46.6, 48.9, 53.1, 64.8, 123.1, 126.9, 128.2, 128.7, 138.5, 141.2, 178.4, 178.9 ppm. *cis*-**2c**: white solid. Mp: 130−131 °C. IR (film) ν_{max}: 3334, 2923, 1775, 1701, 1434, 1383, 1284, 1084, 962, 783 cm^{-1}. ^1H NMR: δ 1.73 (br s, 1H), 2.34 (s, 3H), 2.91 (s, 3H), 3.15 (dd, J = 9.7, 7.0 Hz, 1H), 3.27 (t, J = 7.0 Hz, 1H), 3.32 (t, J = 8.1 Hz, 1H), 3.70 (d, J = 9.7 Hz, 1H), 4.35 (d, J = 8.1 Hz, 1H), 7.07−7.12 (m, 3H), 7.20−7.24 (m, 1H). ^{13}C NMR: δ 21.5, 24.9, 46.0, 49.0, 49.3, 65.6, 124.1, 127.8, 128.1, 128.8, 137.6, 137.8, 175.8, 179.3 ppm. HRMS-ESI calcd for $[C_{14}H_{16}N_2O_2 + Na]^+$ $(M + Na)^+$: 267.1104; found: 267.1105.

(3aS,4S*,6aR*)-2-Methyl-4-(o-tolyl)tetrahydropyrrolo[3,4-c]-pyrrole-1,3(2H,3aH)-dione (trans-**2d**) and (3aS*,4R*,6aR*)-2-Methyl-4-(o-tolyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2d**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1d** (111 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1), cycloadducts *trans*/*cis*-**2d** (95 mg, yield: 78%, *trans*:*cis* = 48:52, determined by ^1H NMR of the crude product). *trans*-**2d**: colorless oil. IR (film) ν_{max}: 3333, 2950, 1774, 1699, 1435, 1383, 1282, 1128, 751 cm^{-1}. ^1H NMR: δ 1.64 (br s, 1H), 2.49 (s, 3H), 3.04 (s, 3H), 3.38−3.48 (m, 4H), 4.88 (s, 1H), 7.18−7.23 (m, 4H). ^{13}C NMR: δ 19.6, 25.3, 46.7, 49.2, 52.2, 62.3, 124.5, 125.9, 127.5, 131.3, 135.9, 139.5, 178.7, 179.1 ppm. *cis*-**2d**: colorless oil. IR (film) ν_{max}: 3334, 2919, 2849, 1775, 1699, 1435, 1383, 1315, 1284, 1084, 755 cm^{-1}. ^1H NMR: δ 1.65 (br s, 1H), 2.43 (s, 3H), 2.86 (s, 3H), 3.16 (dd, J = 9.5, 7.1 Hz, 1H), 3.28 (t, J = 7.1 Hz, 1H), 3.43 (t, J = 8.1 Hz, 1H), 3.73 (d, J = 9.5 Hz, 1H), 4.50 (d, J = 8.1 Hz, 1H), 7.12−7.17 (m, 1H), 7.18−7.22 (m, 2H), 7.35−7.38 (m, 1H). ^{13}C NMR: δ 19.4, 24.9, 46.0, 46.8, 48.7, 62.0, 125.3, 125.9, 127.5, 130.1, 135.5, 136.2, 175.5, 179.4 ppm. HRMS-ESI calcd for $[C_{14}H_{16}N_2O_2 + Na]^+$ $(M + Na)^+$: 267.1104; found: 267.1108.

(3aS,4S*,6aR*)-2-Methyl-4-(4-methoxylphenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2e**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-methoxylphenyl)tetrahydropyrrolo-[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2e**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1e** (119 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1 to 2/1), cycloadducts *trans*/*cis*-**2e** (92 mg, yield: 71%, *trans*:*cis* = 45:55, determined by ^1H NMR of the crude product). *trans*-**2e**: colorless oil. IR (film) ν_{max}: 3332, 2918, 1775, 1699, 1512, 1435, 1383, 1282, 1249, 832 cm^{-1}. ^1H NMR: δ 1.82 (br s, 1H), 3.03 (s, 3H), 3.33−3.43 (m, 4H), 3.81 (s, 3H), 4.61 (d, J = 2.5 Hz, 1H), 6.88−6.92 (m, 2H), 7.28−7.32 (m, 2H). ^{13}C NMR: δ 25.2, 46.6, 48.7, 53.1, 55.3, 64.4, 114.1 (2C), 127.3 (2C), 133.3, 158.9, 178.4, 178.9 ppm. *cis*-**2e**: white solid. Mp: 132−133 °C. IR (film) ν_{max}: 3335, 2927, 2837, 1774, 1698, 1513, 1434, 1383, 1247, 821 cm^{-1}. ^1H NMR: δ 1.79 (br s, 1H), 2.92 (s, 3H), 3.14 (dd, J = 9.6, 6.7 Hz, 1H), 3.24−3.31 (m, 2H), 3.68 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 4.34 (d, J = 7.6 Hz, 1H), 6.85−6.89 (m, 2H), 7.19−7.23 (m, 2H). ^{13}C NMR: δ 24.9, 45.9, 48.9, 49.2, 55.1, 65.2, 113.6 (2C), 128.1 (2C), 129.5, 159.2, 175.9, 179.3 ppm. HRMS-ESI calcd for $[C_{14}H_{16}N_2O_3 + Na]^+$ $(M + Na)^+$: 283.1053; found: 283.1054.

(3aS,4S*,6aR*)-2-Methyl-4-(4-(trifluoromethyl)phenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2f**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-(trifluoromethyl)phenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2f**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1f** (138 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1 to 2/1), cycloadducts *trans*/*cis*-**2f** (136 mg, yield: 91%, *trans*:*cis* = 38:62, determined by ^1H NMR of the crude product). *trans*-**2f**: white solid. Mp: 175−176 °C. IR (film) ν_{max}: 3330, 2917, 1775, 1691, 1435, 1327, 1296, 1157, 1117, 811 cm^{-1}. ^1H NMR: δ 2.05 (br s, 1H), 3.04 (s, 3H), 3.32−3.45 (m, 4H), 4.70 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H). ^{13}C NMR: δ 25.3, 46.8, 49.1, 53.6, 64.5, 124.0 (q, $J_{C,F}$ = 272.0 Hz), 125.7 (q, $J_{C,F}$ = 3.7 Hz, 2C), 126.6 (2C), 129.8 (q, $J_{C,F}$ = 32.5 Hz), 145.3, 178.0, 178.5 ppm. *cis*-**2f**: white solid. Mp: 183−184 °C. IR (film) ν_{max}: 3326, 2917, 2849, 1770, 1699, 1436, 1327, 1285, 1109, 817 cm^{-1}. ^1H NMR: δ 1.89 (br s, 1H), 2.91 (s, 3H), 3.18 (dd, J = 9.6, 7.3 Hz, 1H), 3.30 (t, J = 7.3 Hz, 1H), 3.37 (t, J = 8.0 Hz, 1H), 3.71 (d, J = 9.6 Hz, 1H), 4.43 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 25.0, 45.6, 49.0, 49.2, 65.0, 124.1 (d, $J_{C,F}$ = 272.4 Hz), 125.2 (q, $J_{C,F}$ = 3.7 Hz, 2C), 127.5 (2C), 130.1 (q, $J_{C,F}$ = 32.6 Hz), 141.9, 175.4, 179.0 ppm. HRMS-ESI calcd for $[C_{14}H_{13}F_3N_2O_2 + Na]^+$ $(M + Na)^+$: 321.0821; found: 321.0832.

(3aS,4S*,6aR*)-4-(4-Bromophenyl)-2-methyltetrahydropyrrolo-[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2g**) and (3aS*,4R*,6aR*)-4-(4-Bromophenyl)-2-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3-(2H,3aH)-dione (cis-**2g**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1g** (143 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1 to 2/1), cycloadducts *trans*/*cis*-**2g** (139

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mg, yield: 90%, *trans*:*cis* = 32:68, determined by ^{1}H NMR of the crude product). *trans*-**2g**: white solid. Mp: 107−108 °C. IR (film) ν_{max}: 3330, 2945, 1776, 1699, 1487, 1436, 1384, 1281, 1129, 810 cm^{-1}. ^{1}H NMR: δ 1.78 (br s, 1H), 3.03 (s, 3H), 3.32−3.42 (m, 4H), 4.60 (s, 1H), 7.28−7.32 (m, 2H), 7.47−7.51 (m, 2H). ^{13}C NMR: δ 25.2, 46.7, 48.9, 53.3, 64.4, 121.3, 127.9 (2C), 131.8 (2C), 140.3, 178.1, 178.6 ppm. *cis*-**2g**: white solid. Mp: 165−166 °C. IR (film) ν_{max}: 3337, 2917, 2849, 1776, 1699, 1435, 1384, 1315, 1284, 1087, 1010, 813 cm^{-1}. ^{1}H NMR: δ 1.82 (br s, 1H), 2.91 (s, 3H), 3.15 (dd, J = 9.6, 7.0 Hz, 1H), 3.27 (t, J = 7.0 Hz, 1H), 3.32 (t, J = 8.0 Hz, 1H), 3.69 (d, J = 9.6 Hz, 1H), 4.33 (d, J = 8.0 Hz, 1H), 7.16−7.21 (m, 2H), 7.43−7.47 (m, 2H). ^{13}C NMR: δ 25.0, 45.7, 48.9, 49.1, 64.9, 121.8, 128.8 (2C), 131.4 (2C), 136.8, 175.5, 179.1 ppm. HRMS-ESI calcd for $[C_{13}H_{13}BrN_2O_2 + Na]^+$ (M + Na)$^+$: 331.0053 and 333.0032; found: 331.0061 and 333.0039.

(3aS,4S*,6aR*)-2-Methyl-4-(4-cyanophenyl)tetrahydropyrrolo-[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2h**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-cyanophenyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3-(2H,3aH)-dione (cis-**2h**).* Following general procedure C (amide activation performed at −78 °C for 20 min then at 0 °C for 5 min), the reductive 1,3-dipolar cycloaddition of secondary amide **1h** (116 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 2:1 to 3:1), cycloadducts *trans*/*cis*-**2h** (119 mg, yield: 93%, *trans*:*cis* = 31:69, determined by ^{1}H NMR of the crude product). *trans*-**2h**: white solid. Mp: 176−178 °C. IR (film) ν_{max}: 3329, 2917, 2849, 2228, 1775, 1699, 1436, 1384, 1282, 842 cm^{-1}. ^{1}H NMR: δ 1.83 (br s, 1H), 3.04 (s, 3H), 3.30−3.39 (m, 3H), 3.41−3.46 (m, 1H), 4.68 (s, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H). ^{13}C NMR: δ 25.3, 46.8, 49.2, 53.7, 64.6, 111.4, 118.6, 127.0 (2C), 132.6 (2C), 146.8, 177.8, 178.3 ppm. *cis*-**2h**: white solid. Mp: 192−194 °C. IR (film) ν_{max}: 3334, 2929, 2850, 2226, 1775, 1699, 1434, 1384, 1317, 1285, 823 cm^{-1}. ^{1}H NMR: δ 1.96 (br s, 1H), 2.90 (s, 3H), 3.19 (dd, J = 9.7, 7.5 Hz, 1H), 3.31 (t, J = 7.5 Hz, 1H), 3.38 (t, J = 8.1 Hz, 1H), 3.71 (d, J = 9.7 Hz, 1H), 4.43 (d, J = 8.1 Hz, 1H), 7.43−7.47 (m, 2H), 7.60−7.64 (m, 2H). ^{13}C NMR: δ 25.0, 45.5, 49.0, 49.2, 64.8, 111.7, 118.7, 127.9 (2C), 132.1 (2C), 143.4, 175.3, 178.8 ppm. HRMS-ESI calcd for $[C_{14}H_{13}N_3O_2 + Na]^+$ (M + Na)$^+$: 278.0900; found: 278.0906.

(3aS,4S*,6aR*)-2-Methyl-4-(4-acetoxylphenyl)tetrahydro-pyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2i**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-acetoxylphenyl)tetrahydropyrrolo-[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2i**).* Following general procedure C (amide activation performed at −78 °C for 20 min then at 0 °C for 5 min), the reductive 1,3-dipolar cycloaddition of secondary amide **1i** (133 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 2:1 to 3:1), cycloadducts *trans*/*cis*-**2i** (127 mg, yield: 88%, *trans*:*cis* = 46:54, determined by ^{1}H NMR of the crude product). *trans*-**2i**: colorless oil. IR (film) ν_{max}: 3332, 2918, 1753, 1697, 1507, 1435, 1383, 1282, 1198, 848 cm^{-1}. ^{1}H NMR: δ 1.81 (br s, 1H), 2.30 (s, 3H), 3.03 (s, 3H), 3.33−3.44 (m, 4H), 4.66 (d, J = 2.3 Hz, 1H), 7.06−7.11 (m, 2H), 7.39−7.44 (m, 2H). ^{13}C NMR: δ 21.1, 25.2, 46.7, 48.9, 53.4, 64.4, 121.8 (2C), 127.3 (2C), 138.8, 149.9, 169.5, 178.2, 178.8 ppm. *cis*-**2i**: white solid. Mp: 160−161 °C. IR (film) ν_{max}: 3334, 2917, 2849, 1755, 1699, 1507, 1436, 1384, 1316, 1285, 1194, 834 cm^{-1}. ^{1}H NMR: δ 1.82 (br s, 1H), 2.28 (s, 3H), 2.91 (s, 3H), 3.15 (dd, J = 9.5, 7.2 Hz, 1H), 3.27 (t, J = 7.2 Hz, 1H), 3.32 (t, J = 7.9 Hz, 1H), 3.68 (d, J = 9.5 Hz, 1H), 4.37 (d, J = 7.9 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H). ^{13}C NMR: δ 21.1, 24.9, 45.8, 49.0, 49.2, 65.0, 121.4 (2C), 128.1 (2C), 135.3, 150.2, 169.4, 175.6, 179.2 ppm. HRMS-ESI calcd for $[C_{15}H_{16}N_2O_4 + Na]^+$ (M + Na)$^+$: 311.1002; found: 311.1005.

(3aS,4S*,6aR*)-2-Methyl-4-(4-methoxycarbonylphenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2j**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-methoxycarbonylphenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2j**).* Following general procedure C (amide activation performed at −78 °C for 20 min then at 0 °C for 5 min), the reductive 1,3-dipolar cycloaddition of secondary amide **1j** (133 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 2:1 to 3:1), cycloadducts *trans*/*cis*-**2j** (124 mg, yield: 86%, *trans*:*cis* = 37:63, determined by ^{1}H NMR of the crude product). *trans*-**2j**: white solid. Mp: 117−118 °C. IR (film) ν_{max}: 3332, 2952, 1776, 1700, 1610, 1435, 1384, 1282, 1113, 977, 855 cm^{-1}. ^{1}H NMR: δ 1.90 (br s, 1H), 3.04 (s, 3H), 3.33−3.45 (m, 4H), 3.92 (s, 3H), 4.71 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H). ^{13}C NMR: δ 25.3, 46.7, 49.1, 52.1, 53.4, 64.7, 126.2 (2C), 129.3, 130.1 (2C), 146.4, 166.7, 178.1, 178.6 ppm. *cis*-**2j**: white solid. Mp: 184−185 °C. IR (film) ν_{max}: 3333, 2952, 2842, 1775, 1701, 1610, 1436, 1384, 1281, 1113, 870 cm^{-1}. ^{1}H NMR: δ 1.87 (br s, 1H), 2.89 (s, 3H), 3.18 (dd, J = 9.7, 7.2 Hz, 1H), 3.29 (t, J = 7.2 Hz, 1H), 3.37 (t, J = 8.0 Hz, 1H), 3.71 (d, J = 9.7 Hz, 1H), 3.90 (s, 3H), 4.43 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H). ^{13}C NMR: δ 24.9, 45.7, 49.0, 49.2, 52.0, 65.1, 127.1 (2C), 129.6 (2C), 129.7, 143.1, 166.8, 175.4, 179.0 ppm of HRMS-ESI calcd for $[C_{15}H_{16}N_2O_4 + Na]^+$ (M + Na)$^+$: 311.1002; found: 311.1009.

(3aS,4S*,6aR*)-2-Methyl-4-(4-nitrophenyl)tetrahydropyrrolo-[3,4-c]pyrrole-1,3 (2H,3aH)-dione (trans-**2k**) and (3aS*,4R*,6aR*)-2-Methyl-4-(4-nitrophenyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3-(2H,3aH)-dione (cis-**2k**).* Following general procedure C (amide activation performed at −78 °C for 20 min then at 0 °C for 5 min), the reductive 1,3-dipolar cycloaddition of secondary amide **1k** (126 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 2:1 to 3:1), cycloadducts *trans*/*cis*-**2k** (122 mg, yield: 89%, *trans*:*cis* = 15:85, determined by ^{1}H NMR of the crude product). *trans*-**2k**: white solid. Mp: 138−139 °C. IR (film) ν_{max}: 3329, 2917, 1776, 1698, 1605, 1519, 1436, 1348, 1282, 851, 737 cm^{-1}. ^{1}H NMR: δ 2.07 (br s, 1H), 3.05 (s, 3H), 3.34−3.48 (m, 4H), 4.73 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H). ^{13}C NMR: δ 25.3, 46.8, 49.3, 53.8, 64.5, 124.0 (2C), 127.2 (2C), 147.3, 148.7, 177.7, 178.3 ppm. *cis*-**2k**: white solid. Mp: 206−207 °C. IR (film) ν_{max}: 3357, 2850, 1772, 1699, 1599, 1516, 1436, 1383, 1346, 1286, 1086, 857 cm^{-1}. ^{1}H NMR: δ 2.00 (br s, 1H), 2.90 (s, 3H), 3.21 (dd, J = 9.6, 7.4 Hz, 1H), 3.33 (t, J = 7.4 Hz, 1H), 3.41 (t, J = 8.0 Hz, 1H), 3.73 (d, J = 9.6 Hz, 1H), 4.49 (d, J = 8.0 Hz, 1H), 7.49−7.53 (m, 2H), 8.17−8.21 (m, 2H). ^{13}C NMR: δ 25.0, 45.5, 49.0, 49.2, 64.5, 123.5 (2C), 127.9 (2C), 145.6, 147.5, 175.3, 178.8 ppm. HRMS-ESI calcd for $[C_{13}H_{13}N_3O_4 + Na]^+$ (M + Na)$^+$: 298.0798; found: 298.0800.

(3aS,4S*,6aR*)-2-Methyl-4-(thiophen-2-yl)tetrahydropyrrolo-[3,4-c]pyrrole-1,3 (2H,3aH)-dione (trans-**2l**) and (3aS*,4R*,6aR*)-2-Methyl-4-(thiophen-2-yl)tetrahydropyrrolo[3,4-c]pyrrole1,3 (2H,3aH)-dione (cis-**2l**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1l** (107 mg) with *N*-methylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:1 to 2:1), cycloadducts *trans*/*cis*-**2l** (100 mg, yield: 85%, *trans*:*cis* = 47:53, determined by ^{1}H NMR of the crude product). *trans*-**2l**: colorless oil. IR (film) ν_{max}: 3323, 2945, 1775, 1698, 1435, 1384, 1281, 1234, 1126, 842, 707 cm^{-1}. ^{1}H NMR: δ 2.03 (br s, 1H), 3.02 (s, 3H), 3.35−3.43 (m, 3H), 3.49−3.54 (m, 1H), 4.93 (s, 1H), 6.95−7.00 (m, 2H), 7.21−7.26 (m, 1H). ^{13}C NMR: δ 25.2, 46.0, 48.6, 53.3, 61.1, 124.2, 124.8, 127.1, 145.8, 177.6, 177.8 ppm. *cis*-**2l**: white solid. Mp: 138−139 °C. IR (film) ν_{max}: 3330, 2927, 2849, 1774, 1698, 1435, 1384, 1301, 1090, 830, 707 cm^{-1}. ^{1}H NMR: δ 2.10 (br s, 1H), 2.92 (s, 3H), 3.15 (dd, J = 9.7, 7.0 Hz, 1H), 3.27 (t, J = 7.0 Hz, 1H), 3.32 (t, J = 8.1 Hz, 1H), 3.68 (d, J = 9.7 Hz, 1H), 4.73 (d, J = 8.1 Hz, 1H), 6.99−7.02 (m, 1H), 7.04−7.07 (m, 1H), 7.21−7.25 (m, 1H). ^{13}C NMR: δ 25.0, 46.0, 48.8, 49.5, 61.0, 124.8 (2C), 126.9, 142.0, 175.5, 179.0 ppm. HRMS-ESI calcd for $[C_{11}H_{12}N_2O_2S + Na]^+$ (M + Na)$^+$: 259.0512; found: 259.0518.

(3aS,4S*,6aR*)-2,4-Diphenyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (trans-**2m**) and (3aS*,4R*,6aR*)-2,4-Diphenyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (cis-**2m**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with *N*-phenylmaleimide gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:1 to 2:1), the known cycloadducts *trans*/*cis*-**2m**[19a] (132 mg, yield: 90%, *trans*:*cis* = 48:52, determined by ^{1}H NMR of the crude product). *trans*-**2m**: colorless oil. IR (film) ν_{max}: 3336, 2920, 1774, 1709, 1598, 1497, 1384, 1173, 732 cm^{-1}. ^{1}H NMR: δ 1.72 (br s, 1H), 3.44−3.62 (m, 4H), 4.81 (s, 1H), 7.28−7.52 (m, 10H). ^{13}C NMR: δ 46.6, 49.3, 53.0, 65.4, 126.2 (2C), 126.4 (2C), 127.6, 128.7, 128.8 (2C), 129.2 (2C), 131.8, 141.2, 177.4, 177.9 ppm. *cis*-**2m**: white solid. Mp: 177−178 °C. IR (film) ν_{max}: 3337, 2968,

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2848, 1776, 1711, 1597, 1500, 1384, 1182, 749 cm^{-1}. ^1H NMR: δ 1.97 (br s, 1H), 3.24 (dd, J = 9.6, 6.4 Hz, 1H), 3.41−3.49 (m, 2H), 3.83 (d, J = 9.6 Hz, 1H), 4.50 (d, J = 8.0 Hz, 1H), 7.17−7.20 (m, 2H), 7.27−7.44 (m, 8H). ^{13}C NMR: δ 46.2, 49.3, 49.4, 65.9, 126.2 (2C), 127.1 (2C), 128.2, 128.3, 128.4 (2C), 129.0 (2C), 132.0, 137.8, 174.7, 178.4 ppm. MS (ESI, m/z): 315 $(M + Na)^+$.

Dimethyl (2S,3S*,4R*)-2-Phenylpyrrolidine-3,4-dicarboxylate (trans-**2n**) and Dimethyl (2R*,3S*,4R*)-2-Phenylpyrrolidine-3,4-dicarboxylate (cis-**2n**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with dimethyl maleate gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:1), the known cycloadducts *trans*/*cis*-**2n**[13a] (94 mg, yield: 71%, *trans*:*cis* = 50:50, determined by ^1H NMR of the crude product). *trans*-**2n**: colorless oil. IR (film) ν_{max}: 3345, 2952, 1738, 1436, 1364, 1203, 1029, 759, 701 cm^{-1}. ^1H NMR: δ 1.85 (br s, 1H), 3.18−3.23 (m, 1H), 3.36 (dd, J = 15.5, 7.6 Hz, 1H), 3.41−3.48 (m, 2H), 3.69 (s, 3H), 3.70 (s, 3H), 4.66 (d, J = 6.6 Hz, 1H), 7.23−7.25 (m, 1H), 7.31−7.35 (m, 2H), 7.39−7.43 (m, 2H). ^{13}C NMR: δ 47.7, 49.9, 52.0 (2C), 55.1, 64.7, 126.4 (2C), 127.3, 128.5 (2C), 142.8, 172.2, 173.0 ppm. *cis*-**2n**: white solid. Mp: 61−62 °C. IR (film) ν_{max}: 3360, 2951, 1739, 1436, 1381, 1316, 1209, 1029, 750, 700 cm^{-1}. ^1H NMR: δ 2.42 (br s, 1H), 3.26 (s, 3H), 3.33−3.38 (m, 1H), 3.42−3.48 (m, 1H), 3.58 (dd, J = 7.5, 5.9 Hz, 1H), 3.67 (s, 3H), 3.79 (dd, J = 11.4, 6.4 Hz, 1H), 3.46 (d, J = 5.9 Hz, 1H), 7.23- 7.33 (m, 5H). ^{13}C NMR: δ 47.9, 48.8, 51.3, 52.0, 52.6, 66.9, 126.3 (2C), 127.5, 128.2 (2C), 137.6, 172.2, 172.4 ppm. MS (ESI, m/z): 286 $(M + Na)^+$.

Dimethyl (2S,3S*,4S*)-2-Phenylpyrrolidine-3,4-dicarboxylate (trans-**2o**) and Dimethyl (2R*,3S*,4S*)-2-Phenylpyrrolidine-3,4-dicarboxylate (cis-**2o**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with dimethyl fumarate gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:1), the known cycloadducts *trans*/*cis*-**2o**[13a] as an inseparable mixture (96 mg, yield: 73%, *trans*:*cis* = 50:50, determined by ^1H NMR of the crude product) as a colorless oil. IR (film) ν_{max}: 3341, 2922, 2852, 1728, 1455, 1384, 1163, 1080, 1019, 749, 697 cm^{-1}. ^1H NMR: δ 2.12 (br s, 2H), 3.12 (dd, J = 11.1, 8.3 Hz, 1H), 3.19 (s, 3H), 3.32−3.38 (m, 2H), 3.42−3.47 (m, 2H), 3.50−3.56 (m, 1H), 3.62 (dd, J = 8.1, 5.3 Hz, 1H), 3.67 (s, 3H), 3.71−3.75 (m, 7H), 4.30 (d, J = 8.1 Hz, 1H), 4.54 (d, J = 8.1 Hz, 1H), 7.22−7.37 (m, 8H), 7.39−7.43 (m, 2H). ^{13}C NMR: δ 47.6, 49.1, 50.7, 51.0, 51.4, 52.2 (2C), 52.3, 53.1, 55.2, 66.4, 67.8, 126.7 (2C), 126.9 (2C), 127.5, 127.8, 128.1 (2C), 128.6 (2C), 138.5, 140.8, 172.9, 173.7 (2C), 174.3 ppm. MS (ESI, m/z): 286 $(M + Na)^+$.

(2R,3S*,4S*)-2-Phenylpyrrolidine-3,4-dicarbonitrile (trans-**2p**) and (2S*,3S*,4S*)-2-Phenylpyrrolidine-3,4-dicarbonitrile (cis-**2p**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with fumaronitrile gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:2), the known cycloadducts *trans*/*cis*-**2p**[13a] as an inseparable mixture (82 mg, yield: 83%, *trans*:*cis* = 50:50, determined by ^1H NMR of the crude product) as a white solid. IR (film) ν_{max}: 3331, 2924, 2854, 2244, 1601, 1452, 1377, 1073, 759, 699 cm^{-1}. ^1H NMR: δ 2.27 (br s, 2H), 3.06 (dd, J = 8.4, 6.8 Hz, 1H), 3.33 (dd, J = 10.8, 7.0 Hz, 1H), 3.39−3.52 (m, 3H), 3.57 (dd, J = 6.6, 4.2 Hz, 1H), 3.61 (dd, J = 11.1, 3.9 Hz, 1H), 3.82 (dd, J = 10.8, 8.0 Hz, 1H), 4.35 (d, J = 8.4 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H), 7.36−7.46 (m, 10H). ^{13}C NMR: δ 33.6, 34.2, 41.1, 41.9, 50.2, 50.9, 64.4, 67.8, 117.1, 117.9, 118.6, 119.1, 126.4 (2C), 126.9 (2C), 128.8 (2C), 128.9, 129.0, 129.2 (2C), 136.0, 137.3 ppm. MS (ESI, m/z): 220 $(M + Na)^+$.

Methyl (2R,3R*)-2-Phenylpyrrolidine-3-carboxylate (trans-**2q**) and Methyl (2R*,3S*)-2-Phenylpyrrolidine-3-carboxylate (cis -**2q**).* Following general procedure C, the reductive 1,3-dipolar cycloaddition of secondary amide **1a** (104 mg) with methyl acrylate gave, after flash column chromatography on silica gel (eluent: $MeOH/CH_2Cl_2$ = 1:15), the known cycloadducts *trans*/*cis*-**2q**[23] as inseparable mixture (41 mg, yield: 40%, *trans*:*cis* = 14:86, determined by ^1H NMR of the crude product) as a colorless oil. For *cis*-**2q**, IR (film) ν_{max}: 3338, 3028, 2949, 2849, 1733, 1455, 1436, 1372, 1202, 1168, 748, 700 cm^{-1}. ^1H NMR: δ 2.06−2.17 (m, 1H), 2.21−2.29 (m, 2H), 3.02 (dt, J = 11.0, 8.3 Hz, 1H), 3.22 (s, 3H), 3.29 (td, J = 7.9, 5.2 Hz, 1H), 3.29 (ddd, J = 11.0, 8.4, 3.7 Hz, 1H), 4.37 (d, J = 7.6 Hz, 1H), 7.22−7.33 (m, 5H). ^{13}C NMR: δ 29.6, 46.6, 49.6, 51.1, 66.3, 126.6 (2C), 127.3, 128.1 (2C), 139.3, 174.4 ppm. MS (ESI, m/z): 206 $(M + H)^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01080.

^1H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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