JOC The Journal of Organic Chemistry

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Platinum-Catalyzed Diastereoselective Intramolecular Coupling of Allyl Halides and Hydrazones

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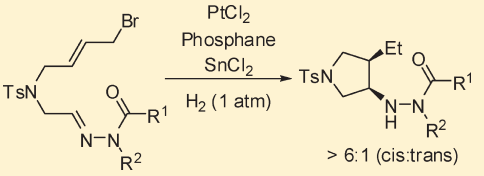
Supporting Information

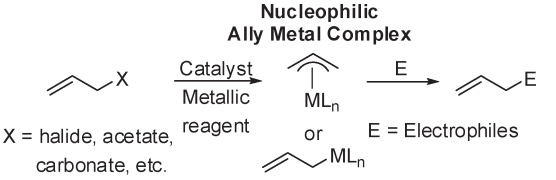
ABSTRACT: Nucleophilic allyl platinum addition to hydrazones under platinum-catalyzed conditions was studied. To generate nucleophilic allyl platinum complexes, allyl halides were employed with platinum complexes, $SnCl_2$, and H_2. The allyl platinum(IV) intermediates reacted with the hydrazone to give the corresponding cyclic amine derivatives in good yield and with excellent diastereoselectivity. The cis selectivity of N-tethered substrates was attributed to a tight interaction of allyl platinum species with the hydrazone, on the basis of the results of solvent screening and acid/base addition experiments.



Allylation of carbonyl and imine compounds is one of the most attractive reactions for the formation of synthetically useful homoallylic alcohols and amines. The general methods employed for the allylation of carbonyl and imine compounds using allyl halides, allyl acetates, or allyl carbonates involve the conversion of electrophilic allylic compounds into nucleophilic allylic species; however, an excess of metallic reagents is required for this conversion (Scheme 1).[1−5] Recently, remarkable improvements have been made to carbonyl allylation, as demonstrated in the diastereo- and enantioselective allylation of aldehydes under transfer hydrogenation conditions, where stoichiometric amounts of metallic reagents are not required for the generation of nucleophilic allyl metal complexes.[6,7] However, imine allylation using allyl halides has not been carried out under catalytic conditions.[5]

Since there are very few examples of the generation and reaction of nucleophilic allyl metal species in the presence of catalytic or less than stoichiometric amounts of metallic reagents, we focus on the catalytic generation of nucleophilic allyl platinum complexes by the use of H_2 and a substoichiometric amount of $SnCl_2$ additives along with platinum complexes. We recently reported the platinum-catalyzed reductive cyclization of allene hydrazones. In this reaction, a nucleophilic allyl platinum intermediate was generated from the hydrometalation of an allene by a $Pt^{II}/SnCl_2$ complex and H_2.[8] In addition to the hydrometalation route shown in the cyclization of allene hydrazones, other synthetic routes to form allyl platinum complexes exhibiting higher reactivity and selectivity have been explored. Herein, we wish to report the first platinum-catalyzed cyclization of allyl halide hydrazones. The most remarkable features of this transformation are as follows: (1) this is the first protocol for the generation of nucleophilic allyl platinum species from allyl halides, H_2, platinum complexes, and $SnCl_2$; (2) $SnCl_2$ used in this transformation is thought to react with a platinum complex to afford catalytically competent platinum species and not to form Sn allyl intermediates; (3) high levels of diastereoselectivity are observed for a wide range of substrates.

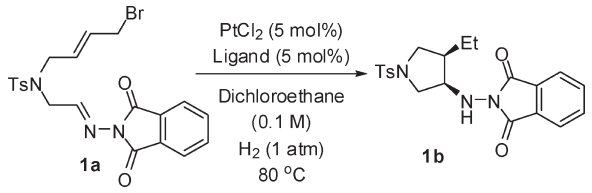
Scheme 1. Formation and Reactions of Nucleophilic Allyl Metal Complexes



The optimization results obtained for **1a** are given in Table 1. The cyclization of **1a** with $PtCl_2$ (5 mol %), $P(C_6H_4\text{-}p\text{-}CF_3)_3$ (5 mol %), and $SnCl_2$ (25 mol %) in dichloroethane (0.1 M) at 80 °C and under 1 atm of H_2 was unsuccessful (entry 1). Similarly, the platinum catalyst with $P(2\text{-furyl})_3$ did not promote the desired allylic cyclization (entry 2). When electron-rich phosphanes were used instead of $P(C_6H_4\text{-}p\text{-}CF_3)_3$ and $P(2\text{-furyl})_3$, **1b** was obtained in higher yields (entries 3−6) with good cis diastereoselectivity. The stereochemical assignment of **1b** was accomplished by comparing its ^1H NMR spectrum with that of a previously reported compound after chemical modification.[8−10] Although **1b** was derived from **1c** under hydrogenation conditions, reduction of the latter could not be controlled in the presence of a platinum catalyst and H_2. The reaction with PCy_3 only showed **1c** in 9% yield with **1b**. To verify the role of $SnCl_2$ in allylic cyclization, 5 mol % of $SnCl_2$ was used, and **1b** was formed in 50% yield (entry 7), indicating that the formation of stoichiometric amounts of allyl Sn complex is not required to afford **1b**. No cyclization occurred in the absence of $SnCl_2$ (entry 8). Because indium-mediated intermolecular allylation of imines is known to proceed even in the absence of transition-metal catalysts,[5b] cyclization of **1a**

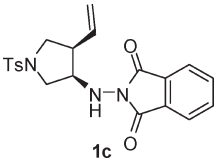
Received: May 19, 2011
Published: June 30, 2011

Table 1. Optimization of the Reductive Cyclization of 1a



entry	ligand	amt of $SnCl_2$ (mol %)	yield of **1b** (%)	cis:trans
1	$P(C_6H_4\text{-}p\text{-}CF_3)_3$	25	0	
2	$P(2\text{-furyl})_3$	25	0	
3	$P(C_6H_4\text{-}p\text{-}OMe)_3$	2	37	4:1
4	$P(C_6H_4\text{-}o\text{-}OMe)_3$	25	41	6:1
5	PCy_3	25	26[a]	5:1
6	**$P(C_6H_2\text{-}OMe_3)_3$**	**25**	**82**	**6:1**
7	$P(C_6H_2\text{-}OMe_3)_3$	5	50	5:1
8	$P(C_6H_2\text{-}OMe_3)_3$	0	0	
9	$P(C_6H_2\text{-}OMe_3)_3$	25	0[b]	

[a] The olefinated product **1c** was observed (**1b**, 26%; **1c**, 9%).

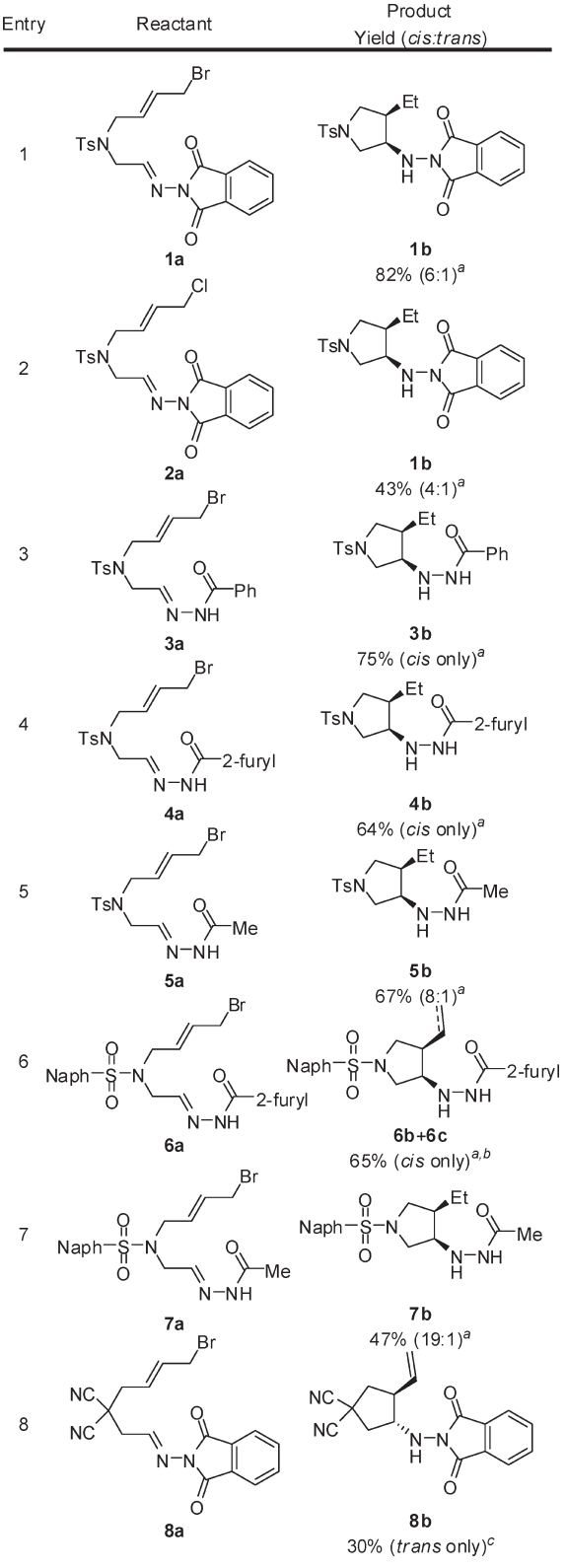


[b] No H_2.

was attempted in the presence of $SnCl_2$ but without using any platinum complex; however, cyclization did not occur in this case. On the basis of the aforementioned experimental results, we could speculate that the catalytically competent complex formed in the aforementioned reaction was a stannane-coordinated platinum complex. The cyclization of the allyl stannane complex with the hydrazone was excluded. Next, the role of H_2 in allylic cyclization was evaluated. The reaction carried out in the absence of H_2 afforded no product (entry 9), indicating that H_2 was critical for the catalytic turnover of the cyclization. Reactions carried out in the presence of other metal catalysts such as $PdCl_2$, $NiCl_2$, $AuCl_3$, $RuCl_2(PPh_3)_3$, and $Pt(acac)_2$ did not afford the desired product.

The substrate scope of the allylic cyclization reaction was evaluated by comparing the results obtained for different allyl groups such as allyl bromides, allyl chlorides, and allyl acetates (Table 2). Substrate **2a**, which had an allyl chloride group, participated in the cyclization reaction to afford the product **1b** in 43% yield and a cis:trans ratio of 4:1. The poor yield of the reaction could be attributed to the fact that chloride is a poorer leaving group than bromide. Another substrate possessing an allyl acetate group did not participate in the reaction. Next, substrates possessing different hydrazones were subjected to cyclization under the indicated reaction conditions. Cyclization of **3a**, which had a benzoyl-substituted hydrazone, proceeded smoothly to afford *cis*-**3b** as the only product in 75% yield. Compounds **4a** and **5a** afforded the corresponding products **4b** (yield 64%) and **5b** (yield 67%), respectively. When the tosyl group on the nitrogen atom was replaced with a naphthalene sulfonyl group, cyclized product **6c** without over-reduction was detected as a mixture with **6b**, and in the case of **7b**, increased

Table 2. Examples of Cyclization of Allyl Halide Hydrazones



[a] $P(C_6H_2\text{-}OMe_3)_3$. [b] **6b** (40%) and **6c** (25%). [c] $P(C_6H_4\text{-}p\text{-}CF_3)_3$.

diastereoselectivity was observed. The carbon-tethered substrate **8a** underwent the cyclization in the presence of electron-deficient $P(C_6H_4\text{-}p\text{-}CF_3)_3$ to afford *trans*-**8b** in 30% yield. In the case

dx.doi.org/10.1021/jo200993v |J. Org. Chem. 2011, 76, 6877–6882

of six-membered rings, the desired cyclized products were not obtained under the current conditions.

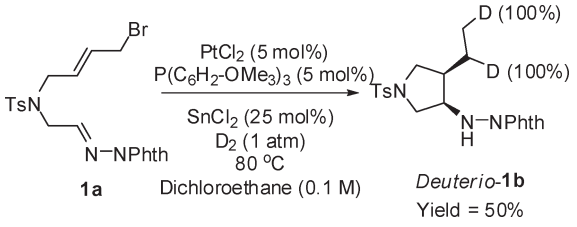
To gain an insight into the reaction mechanism, a deuterium-labeling experiment was conducted (Scheme 2). The experimental results revealed that deuterium atoms were incorporated into the ethyl group, as illustrated for *deuterio*-**1b**, thus implying that the transformation proceeded via tandem platinum-catalyzed allylic cyclization and subsequent alkene reduction.

The cyclization mechanism proposed on the basis of the deuterium-labeling experiment is illustrated in Scheme 3. The platinum hydride $Pt^{II}H(PR_3)(SnCl_3)$ is presumed to be derived from $PtCl_2$, $SnCl_2$, PR_3, and H_2.[11] Because the reaction does not occur in the absence of H_2, the platinum hydride appears to promote this transformation. Upon the addition of the platinum hydride species to the allyl bromide, allyl platinum(IV) complex **I** is formed via oxidative addition.[12,13] Subsequent allylation of the hydrazone affords the cyclic intermediate **II**, which is converted into the isomer **1c** with the concomitant release of $Pt^{II}Br(PR_3)(SnCl_3)$. In the presence of H_2, **1c** undergoes reduction to afford **1b**, and $Pt^{II}H(PR_3)(SnCl_3)$ is regenerated with a release of HBr. Alternatively, reductive elimination of intermediate **II** provides $Pt^{II}H(PR_3)(SnCl_3)$ and N-brominated **1b** or **1c** which is converted into **1b** or **1c** after the workup.

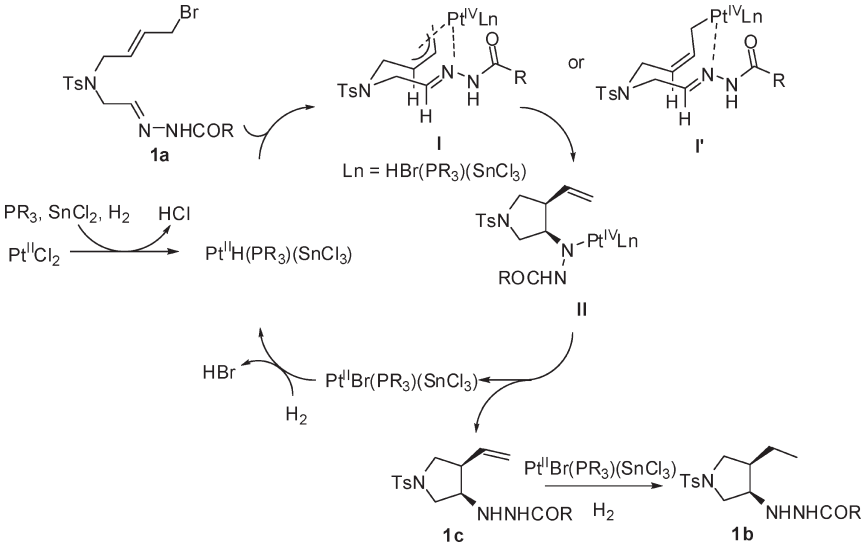
In the case of N-tethered substrates, the strong coordination between the hydrazone and allyl platinum moieties (intermediate **I** or **I′**) is presumed to lead to the exclusive formation of cis diastereomers.[5a] As illustrated in the substrate scope (Table 2), an N-acyl hydrazone group which has a high affinity for metal species is the prerequisite for high yield and diastereoselectivity in this transformation. In addition, the following solvent screening experiments support the hypothesis that the strong interaction between the allyl platinum complex and the hydrazone moiety is the key factor that promotes highly diastereoselective cyclization. The amount of the trans product **1b** increases when polar coordinating solvents are used (cis:trans = 6:1 with dichloroethane, cis:trans = 4:1 with CH_3CN, and cis:trans = 3:1 with THF).[14] Remarkably, cyclization of **1a** proceeds readily in DMF (80 °C) to afford **1c** with a cis:trans ratio of 1:1, without over-reduction. At elevated temperatures (152 °C), the major diastereomer is reversed (cis:trans = 1:3), implying that the coordination between the allyl platinum species and the hydrazone is destroyed in DMF at high temperatures.

In our previous report on the reductive cyclization of allene hydrazones, we have proposed a similar catalytic cycle where the trans isomer is obtained as the major product without over-reduction when an allyl platinum(II) complex is added to a hydrazone. To account for different product distribution and sterochemical outcomes between the cyclization of allene hydrazones and allyl bromide hydrazones, the following experiments were conducted (Scheme 4). Compound **1d** was subject to the optimized conditions for compound **1a**, which involved $PtCl_2$ (5 mol %), $P(C_6H_2\text{-}OMe_3)_3$ (5 mol %), and $SnCl_2$ (25 mol %) in dichloroethane (0.1 M) at 80 °C under 1 atm of H_2, to provide trans isomers **1b**,**c** as a mixture in 21% and 20% yields, respectively. As the amount of $P(C_6H_2\text{-}OMe_3)_3$ was increased to 10 mol %, only the over-reduction product *trans*-**1b** was observed in 31% yield. In the presence of 10 mol % of $P(C_6H_4\text{-}p\text{-}CF_3)_3$, optimized conditions for compound **1d**, no over-reduction was detected, implying that reduction of **1c** to **1b** might be related to the electronic properties and quantities of phosphane ligands. To account for the completely reversed diastereoselectivity of N-tethered substrates between these processes, the ligand effect on each allyl platinum complex was considered. Presumably, hydride and bromide ligands of intermediate **I** in Scheme 3 might play a key role to afford the cis product. To confirm this hypothesis, the effect of acid additives in the cyclization of allene hydrazones was evaluated. Gratifyingly, in the presence of acid additives, the amount of cis cyclized products in the cyclization of allene hydrazones was dramatically increased (cis:trans = 4:1

Scheme 2. Deuterium-Labeling Study

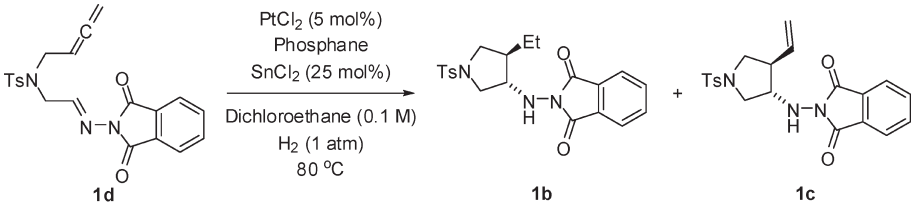


Scheme 3. Plausible Catalytic Cycle



dx.doi.org/10.1021/jo200993v |*J. Org. Chem.* 2011, 76, 6877–6882

Scheme 4. Effects of Phosphane Ligands and Acid Additives in the Cyclization of 1d



$P(C_6H_2\text{-}OMe_3)_3$ (5 mol%), Yield = 21% (**1b**), 20% (**1c**) *trans* only
$P(C_6H_2\text{-}OMe_3)_3$ (10 mol%), Yield = 31% (**1b**) *trans* only
$P(C_6H_4\text{-}p CF_3)_3$ (10 mol%), Yield = 69% (**1c**) *cis*:*trans* (1:8)
$P(C_6H_2\text{-}OMe_3)_3$ (5 mol%) & TsOH (100 mol%), Yield = 27% (**1b**) *cis*:*trans* (4:1)

with TsOH). The acid additives might undergo oxidative addition to allyl platinum(II) species to afford allyl platinum(IV) complexes which are intermediates similar to those proposed in Scheme 3.[15] The effect of base additives in the cyclization of **1a** was evaluated. In the presence of 50 mol % of $NaHCO_3$, the amount of *trans*-**1b** was increased (cis:trans = 2.5:1 with $NaHCO_3$ and cis:trans = 6:1 without base). According to the results of control experiments, it is presumed that the different stereochemical outcomes of the cyclization of allyl bromide hydrazones and allene hydrazones stem from different allyl platinum intermediates ((allyl)$Pt^{IV}HBr(PR_3)(SnCl_3)$ and (allyl)$Pt^{II}(PR_3)(SnCl_3)$).

In conclusion, we have demonstrated a diastereoselective route to functionalized carbocyclic and heterocyclic amines via a nucleophilic allyl platinum intermediate, which is generated by the reaction between an allyl halide, a platinum complex, $SnCl_2$, and H_2. It is noteworthy that stereoselective allylation of hydrazones proceeds even in the absence of preformed allyl metal reagents derived from large quantities of metal reagents. In addition, this transformation may offer complementary and improved reaction conditions so that cyclic amines can be formed with stereoselectivity tbetter han that in the platinum-catalyzed reductive cyclization of allene hydrazones. On the basis of base addition experiments using allyl bromide hydrazones and acid addition experiments using allene hydrazones, the opposite stereochemical outcomes of N-tethered substrates and improved diastereoselectivity of C-tethered substrate are thought to be related to the reactivity differences between (allyl)$Pt^{IV}HBr(PR_3)$-$(SnCl_3)$ and (allyl)$Pt^{II}(PR_3)(SnCl_3)$.

EXPERIMENTAL SECTION

Representative Experimental Procedure for Cyclization of Allyl bromide-Hydrazones. To a premixed solution of $PtCl_2$ (5 mol %), phosphane (5 mol %), and $SnCl_2$ (25 mol %) under H_2 (1 atm) in dichloroethane (0.1 M) was added the starting material under H_2 (1 atm) at room temperature. The resulting mixture was allowed to run at 80 °C until the starting material was completely consumed.

Representative Experimental Procedure for Reduction of *cis*- and *trans*-1c and 3c. To a solution of Pd/C (30 wt %) in methanol or ethanol (0.01 M) was added **1c** or **3c** under H_2 (1 atm) at room temperature. The resulting mixture was run at ambient temperature for 18 h.

***cis*-2-(4-Ethyl-1-tosylpyrrolidin-3-ylamino)isoindoline-1,3-dione (*cis*-1b).** The representative experimental procedure was applied to compound **1a** (61.1 mg, 0.125 mmol) to yield the product **1b** (42.3 mg, 82%, reaction time 2 h). The stereochemical assignment of *cis*-**1b** was confirmed by comparison to a sample prepared by the following method. The palladium-catalyzed stannylative cyclization of allene-hydrazone **1d** (0.65 g, 1.59 mmol) was conducted by a procedure reported in ref 9 to afford stannane-incorporated *cis*-2-(1-tosyl-4-(1-(trimethylstannyl)vinyl)pyrrolidin-3-ylamino)isoindoline-1,3-dione in 20% yield (0.18 g). Destannylation of the resulting cyclic compound (60 mg, 0.1 mmol) was performed with 1 M HCl in ether solution to form *cis*-**1c**[8] (22 mg, 53.5% yield). The representative reduction procedure was applied to compound *cis*-**1c** (22 mg, 0.053 mmol) to yield product *cis*-**1b** (13 mg, 59%), which showed a ^{1}H NMR spectrum identical with that of cyclized product **1b** formed by our methodology. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.80 (m, 2H), 7.78−7.72 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 4.39 (d, J = 4.0 Hz, 1H), 3.58−3.54 (m, 1H), 3.50−3.45 (m, 2H), 3.18 (dd, J = 8.0, 13.6 Hz, 1H), 3.04 (dd, J = 6.0, 10.0 Hz, 1H), 2.42 (s, 3H), 1.96−1.88 (m, 1H), 1.57−1.46 (m, 1H), 1.23−1.19 (m, 1H), 0.88 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 143.6, 134.6, 133.4, 130.0, 129.7, 123.7, 122.7, 64.6, 52.1, 51.6, 44.5, 25.1, 21.9, 12.3. HRMS: m/z calcd for $C_{21}H_{23}N_3O_4S$ $[M + 1]^+$ 414.1488, found 414.1490. IR (neat): 3299, 2961, 2926, 2876, 1723, 1632, 1385, 1340, 1196, 1161, 1061 cm^{-1}.

***deuterio-cis*-2-(4-Ethyl-1-tosylpyrrolidin-3-ylamino)isoindoline-1,3-dione (*deuterio-cis*-1b).** The representative experimental procedure was applied to compound **1a** (61.1 mg, 0.125 mmol) to yield the product *deuterio*-**1b** (26 mg, 50%, reaction time 2 h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.83 (m, 2H), 7.76−7.73 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 4.39 (d, J = 3.2 Hz, 1H), 3.57−3.48 (m, 3H), 3.18 (dd, J = 6.0, 10.0 Hz, 1H), 3.04 (dd, J = 5.6, 9.6 Hz, 1H), 2.42 (s, 3H), 1.93−1.91 (m, 1H), 1.54−1.48 (m, 0.5 H), 1.26−1.20 (m, 0.5 H), 0.85 (t, J = 7.2 Hz, 2H).

***trans*-2-(4-Ethyl-1-tosylpyrrolidin-3-ylamino)isoindoline-1,3-dione (*trans*-1b).** The platinum-catalyzed hydrogenative cyclization of allene hydrazone **1d** was conducted by a procedure reported in ref 8 to afford *trans*-**1c**.[8] The representative reduction procedure was applied to *trans*-**1c** (42.6 mg, 0.103 mmol) to yield *trans*-**1b** (21 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.74 (m, 6H), 7.34 (d, J = 8.4 Hz, 2H), 4.40 (d, J = 4.0 Hz, 1H), 3.74−3.80 (m, 1H), 3.58−3.38 (m, 3H), 3.10 (t, J = 9.6 Hz, 1H), 2.44 (s, 3H), 2.15−2.08 (m, 1H), 1.72−1.63 (m, 1H), 1.45−1.34 (m, 1H), 1.01 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 143.5, 134.6, 130.1, 129.8, 127.8, 123.8, 123.7, 61.1, 52.9, 50.7, 44.5, 22.0, 19.9, 12.9. HRMS: m/z calcd for $C_{21}H_{23}N_3O_4S$ $[M + 1]^+$ 414.1488, found 414.1486. IR (neat): 3062, 2961, 2926, 1787, 1725, 1598, 1467, 1385, 1342, 1162, 1094, 1048 cm^{-1}.

***cis*-*N*′-(4-Ethyl-1-tosylpyrrolidin-3-yl)benzohydrazide (*cis*-3b).** The representative experimental procedure was applied to compound **3a** (58 mg, 0.125 mmol) to yield the product **3b** (36.3 mg, 75%, reaction time 1 h). Stereochemical assignment of *cis*-**3b** was confirmed by comparison to the ^{1}H NMR of *trans*-**3b**. 1D NOE experiments using both *trans*- and *cis*-**3b** were carried out, showing a weak NOE interaction (<2%) in the Supporting Information. ^{1}H NMR

dx.doi.org/10.1021/jo200993v |*J. Org. Chem.* 2011, 76, 6877–6882

(500 MHz, $CDCl_3$): δ 7.74−7.69 (m, 4H), 7.56 (s, 1H), 7.55−7.52 (m, 1H), 7.45−7.42 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.67 (s, 1H), 3.56 (dd, J = 6.8, 9.6 Hz, 1H), 3.42−3.39 (m, 1H), 3.40−3.26 (m, 2H), 2.97 (dd, J = 5.2, 10.0 Hz, 1H), 2.42 (s, 3H), 1.90−1.87 (m, 1H), 1.44−1.38 (m, 1H), 1.16−1.11 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 143.6, 133.6, 132.3, 129.7, 128.9, 127.7, 127.0, 64.4, 51.9, 51.5, 44.7, 25.2, 21.9, 12.5. HRMS: m/z calcd for $C_{20}H_{25}N_3O_3S$ [M$^+$] 387.1617, found 387.1619. IR (neat): 3362, 2959, 2923, 2854, 1725, 1645, 1462, 1339, 1196, 1160, 1092 cm^{-1}.

***trans*-*N*′-(4-Ethyl-1-tosylpyrrolidin-3-yl)benzohydrazide (*trans*-3b).** The platinum-catalyzed hydrogenative cyclization of allene hydrazone was conducted by a procedure reported in ref 8 to afford *trans*-**3c**. The representative reduction procedure was applied to the compound *trans*-**3c** (18 mg, 0.046 mmol) to yield the product *trans*-**3b** (13 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.68−7.66 (m, 2H), 7.56−7.53 (m, 1H), 7.47−7.44 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 4.55 (s, 1H), 3.65 (s, 1H), 3.54−3.50 (m, 2H), 3.24 (dd, J = 4.1, 9.1 Hz, 1H), 3.21−3.17 (m, 1H), 2.40 (s, 3H), 2.04−2.02 (m, 1H), 1.57−1.53 (m, 1H), 1.46−1.43 (m, 1H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 143.6, 135.0, 132.5, 132.4, 129.8, 129.0, 127.8, 127.0, 59.7, 52.2, 51.5, 44.7, 21.7, 19.8, 12.7. HRMS: m/z calcd for $C_{20}H_{25}N_3O_3S$ [M + 1]$^+$ 388.1695, found 388.1697. IR (neat): 3362, 2963, 2929, 2872, 1645, 1462, 1337, 1196, 1161, 1096 cm^{-1}.

***cis*-*N*′-(4-Ethyl-1-tosylpyrrolidin-3-yl)furan-2-carbohydrazide (4b).** The representative experimental procedure was applied to compound **4a** (56.6 mg, 0.125 mmol) to yield the product **4b** (30.1 mg, 64%, reaction time 1 h). The stereochemical assignment for *cis*-**4b** was made by analogy of its ^{1}H NMR with that of **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.45 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 3.2 Hz, 1H), 6.52−6.50 (m, 1H), 4.49 (s, 1H), 3.52 (dd, J = 7.2, 9.6 Hz, 1H), 3.40−3.67 (m, 1H), 3.33−3.29 (m, 1H), 3.24 (dd, J = 3.6, 10.8 Hz, 1H), 2.98 (dd, J = 5.2, 10.0 Hz, 1H), 2.42 (s, 3H), 1.89−1.82 (m, 1H), 1.43−1.36 (m, 1H), 1.16−1.09 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 146.3, 144.5, 143.6, 133.4, 129.7, 115.4, 112.3, 64.4, 51.8, 51.3, 44.6, 25.0, 21.9, 12.4. HRMS: m/z calcd for $C_{18}H_{23}N_3O_4S$ [M + 1]$^+$ 378.1488, found 378.1490. IR (neat): 3298, 2961, 2926, 2876, 1650, 1593, 1466, 1337, 1160, 1092 cm^{-1}.

***cis*-*N*′-(4-Ethyl-1-tosylpyrrolidin-3-yl)acetohydrazide (5b).** The representative experimental procedure was applied to compound **5a** (50 mg, 0.125 mmol) to yield the product **5b** (27.1 mg, 67%, reaction time 1.5 h). The stereochemical assignment for *cis*-**5b** was made by analogy of its ^{1}H NMR with that of **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 6.8 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.10 (s, 1H), 4.41 (s, 1H), 3.51−3.44 (m, 1H), 3.28−3.17 (m, 3H), 2.91 (dd, J = 4.8, 9.2 Hz, 1H), 2.41 (s, 3H), 1.91 (s, 3H), 1.84−1.76 (m, 1H), 1.37−1.29 (m, 1H), 1.10−1.03 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 143.7, 133.1, 129.7, 127.7, 64.3, 51.9, 51.5, 44.4, 25.1, 21.9,21.4, 12.4. HRMS: m/z calcd for $C_{15}H_{23}N_3O_3S$ [M + 1]$^+$ 326.1538, found 326.1541. IR (neat): 3381, 2963, 2931, 2882, 1650, 1466, 1336, 1160, 1093 cm^{-1}.

***cis*-*N*′-(1-(Naphthalen-2-ylsulfonyl)-4-vinylpyrrolidin-3-yl)-furan-2-carbohydrazide (6c) and *cis*-*N*′-(4-Ethyl-1-(naphthalen-2-ylsulfonyl)pyrrolidin-3-yl)furan-2-carbohydrazide (6b).** The representative experimental procedure was applied to compound **6a** (122 mg, 0.25 mmol) to yield the products **6b,c** as an inseparable mixture (67.1 mg, 65%, reaction time 2 h). The stereochemical assignment for *cis*-**6b** was made by analogy of its ^{1}H NMR with that of **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.00−7.93 (m, 2H), 7.92 (d, J = 7.6 Hz, 1H), 7.86−7.84 (m, 1H), 7.67−7.59 (m, 2H), 7.40 (s, 1H), 7.09−7.08 (m, 1H), 6.49−6.48 (m, 1H) 5.64−5.55 (m, 1H × 0.38 minor), 5.15−5.04 (m, 2H × 0.38 minor), 4.60 (bs, 1H), 3.61−3.53 (m, 2H), 3.48−3.07 (m, 3H), 2.65−2.62 (m, 1H ×x 0.38 minor), 1.88 (bs, 1H × 0.62 major), 1.41−1.33 (m, 1H × 0.62 major), 1.16−1.08 (m, 1H × 0.62 major), 0.85 (t, J = 7.6 Hz, 3H × 0.62 major). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.9, 146.4, 144.7, 135.7, 135.0, 134.1, 134.0, 129.5, 129.4, 129.3, 129.0, 128.9, 128.1, 127.7, 123.2, 123.1, 118.0, 115.5, 115.4, 112.3, 64.5, 64.0, 51.8, 51.5, 51.4, 51.3, 46.7, 44.6, 24.9, 12.2. HRMS: m/z calcd for $C_{21}H_{21}N_3O_4S$ [M + 1]$^+$ 412.1331, found 412.1330; calcd for $C_{21}H_{23}N_3O_4S$ [M + 1]$^+$ 414.1488, found 414.1489. IR (neat): 3345, 3056, 2960, 2926, 2856, 1659, 1590, 1474, 1337, 1160, 1131, 1076 cm^{-1}.

***cis*-*N*′-(4-Ethyl-1-(naphthalen-2-ylsulfonyl)pyrrolidin-3-yl)-acetohydrazide (7b).** The representative experimental procedure was applied to compound **7a** (109 mg, 0.25 mmol) to yield the product **7b** (42.4 mg, 47%, reaction time 3 h). The stereochemical assignment for *cis*-**7b** was made by analogy of its ^{1}H NMR with that of **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.00−7.97 (m, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.68−7.62 (m, 2H), 7.11 (s, 1H), 3.58 (dd, J = 7.2, 10.0 Hz, 1H), 3.30 (s, 3H), 3.01 (dd, J = 4.8, 9.6 Hz, 1H), 1.86 (s, 3H), 1.36−1.29 (m, 1H), 1.09−1.02 (m, 1H), 0.82 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 135.1, 134.0, 132.4, 129.5, 129.4, 129.0, 128.9, 128.2, 127.8, 123.2, 64.3, 51.8, 51.4, 44.6, 24.9, 21.2, 12.2. HRMS: m/z calcd for $C_{18}H_{23}N_3O_3S$ [M + 1]$^+$ 362.1538, found 362.1541. IR (neat): 3288, 3057, 2961, 2929, 2876, 1659, 1462, 1336, 1160, 1131, 1077 cm^{-1}.

***trans*-3-(1,3-Dioxoisoindolin-2-ylamino)-4-vinylcyclopentane-1,1-dicarbonitrile (8b).** The representative experimental procedure was applied to compound **8a** (96 mg, 0.25 mmol) to yield the product *trans*-**8b** (23.3 mg, 30%, reaction time 44 h). The stereochemical assignment for *trans*-**8b** was made by comparing the ^{1}H NMR of a *cis*- and *trans*-**3b** mixture, which was prepared by the platinum-catalyzed hydrogenative cyclization of allene hydrazone reported in ref 8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.85 (m, 2H), 7.77−7.75 (m, 2H), 6.09−6.00 (m, 1H), 5.43−5.35 (m, 2H), 4.52 (s, 1H), 3.97−3.94 (m, 1H), 3.16−3.09 (m, 1H), 2.95−2.88 (m, 1H), 2.79−2.71 (m, 2H), 2.57 (dd, J = 5.2, 14.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 134.8, 132.1, 130.2, 123.9, 120.8, 117.5, 116.3, 61.6, 46.4, 43.8, 41.2, 31.4. HRMS: m/z calcd for $C_{17}H_{14}N_4O_2$ [M + 1]$^+$ 307.1195, found 307.1199. IR (neat): 3295, 2963, 2926, 2837, 1723, 1643, 1467, 1383, 1197, 1119, 1077 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. A table giving solvent screening results and figures giving spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This study was supported by the Korea Research Foundation (Grant Nos. 2010-0029617, 2010-0016079, and 2010-0002396). We wish to thank the Korean Basic Science Institute (Deagu) for the mass spectra.

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