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CATALYTIC AND DIASTEREOSELECTIVE CASCADE REACTION FOR THE PREPARATION OF *cis*-1,3-DISUBSTITUTED ISOINDOLINE-AMINAL HYBRID COMPOUNDS

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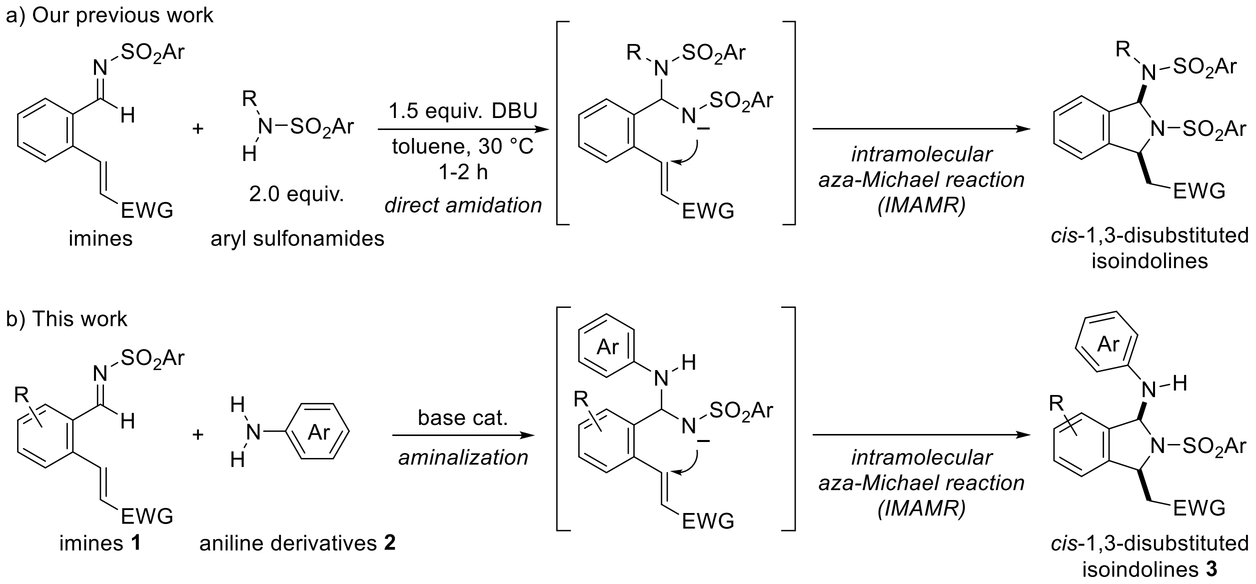
Abstract – A convenient and catalytic method for the diastereoselective construction of *cis*-1,3-disubstituted isoindoline skeletons is described. In the presence of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene as a base catalyst and under mild conditions, the direct aminalization of *N*-protected imines bearing a Michael acceptor using the aniline derivatives and the subsequent intramolecular aza-Michael reaction proceeded successfully in a short reaction time. A series of *cis*-1,3-disubstituted isoindoline-aminal hybrid compounds are obtained in moderate to good yield (44%–93%) with complete diastereocontrol.

Cascade, domino, and related sequential reactions are effective synthetic methods for constructing the structurally complex molecules.[1] In these processes, the reaction systems must be properly designed so that the reaction intermediates can react smoothly in the following phases of the cascade reactions. Aryl aldimines with a Michael acceptor in their *ortho* position have been employed as such in the 1,2-additions/intramolecular aza-Michael cascade reactions for the efficient preparation of 1,3-disubstituted isoindolines.[2,3] Considering the potential application of isoindoline skeletons in several biologically active molecules, natural products, and pharmaceuticals,[4] the development of a novel synthetic approach of isoindoline scaffolds for the diversity-oriented syntheses of various derivatives would be beneficial in organic and medicinal chemistry.

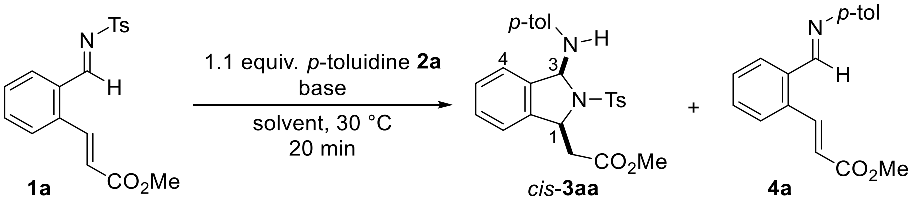
Previously, we reported a novel cascade reaction for the diastereoselective preparation of 1,3-disubstituted isoindolines using nitrogenous nucleophiles in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) as the base promoter (Scheme 1a).[5] Only carbon-based nucleophiles were utilized to achieve the initial 1,2-additions in the cascade processes associated with the formation of 1,3-disubstituted isoindoline skeletons.[2] Thus, the employment of nitrogenous nucleophiles opened up the way to 1,3-disubstituted isoindoline-aminal hybrid compounds. For the first time, the aryl sulfonamide derivatives have been successfully applied as the nitrogen-based nucleophile in our previous work. We envisaged that a cascade process using nitrogenous nucleophiles without protective groups could be achieved by using nitrogenous nucleophiles with appropriate nucleophilicity. Hence, in this paper, we extended our previous findings to investigate the applicability of aniline derivatives as the nitrogenous nucleophiles and to establish the optimal catalytic conditions through trials (Scheme 1b).



Scheme 1. Schematic Representation of the 1,2-Addition/Intramolecular Aza-Michael Cascade Reactions

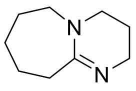
To begin with, the reaction conditions for the aminalization/intramolecular aza-Michael reaction (IMAMR) of imine **1a** with *p*-toluidine **2a** were investigated by using various bases and solvents (Table 1). Based on the previous reaction conditions we studied,[5] the treatment of **1a** with 1.1 equiv. of **2a** in the presence of 1.0 equiv. of DBU in toluene at 30 °C furnished the desired *cis*-**3aa** in 66% yield (entry 1). Under these reaction conditions, undesired imine **4a** was also formed in 14% yield via imine exchange from **1a** and **2a**. Upon conducting the reaction with 1,1,3,3-tetramethylguanidine (TMG) under otherwise identical conditions, the yield of *cis*-**3aa** was not improved (entry 2). When a more basic 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[6] was employed, the yield of *cis*-**3aa** exhibited slight improvement (entry 3). In contrast, other strong bases such as P2-*t*-Bu and KO*t*-Bu were found ineffective (entries 4 and 5). Encouraged by the result of entry 3, the effect of solvent on improving the yield of *cis*-**3aa** was investigated (entries 6–11). To our delight, the desired *cis*-**3aa** was obtained in 85% yield when the cascade reaction was conducted in MeCN (entry 9). Reducing the amount of MTBD proceeded the desired reaction cleanly and the yield of *cis*-**3aa** was further improved. Thus, *cis*-**3aa** was obtained in 90% yield (89% isolated yield) in the presence of 20 mol% of MTBD (entry 12). Although 10 mol% of MTBD produced *cis*-**3aa** in 82% yield, 20 mol% of MTBD was selected as the optimal catalytic amount considering the slightly higher yield of *cis*-**3aa** (entries 12 and 13). The structure and relative configuration of 1,3-disubstituted isoindoline *cis*-**3aa** were identified by NMR, HRMS, IR and 2D-NMR analysis.[7] This stereochemical outcome of *cis*-**3aa** is in good agreement with our previous study in which *p*-toluenesulfonamide was used as a nitrogenous nucleophile.[5] The position of the *p*-tolylamino group, which is involved in the progress of this cascade reaction, was determined by the NOE correlation between the aromatic protons in the *p*-tolyl group and the aromatic proton at 4-position in the isoindoline skeleton.[8]

Table 1. Effect of Bases and Solvents on the Aminalization/Aza-Michael Cascade Reaction of **1a**[a]

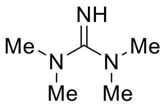


Entry	Base (equiv.)	Solvent	*cis*-**3aa**/%[b]	**4a**/%[b]
1	DBU (1.0)	toluene	66	14
2	TMG (1.0)	toluene	64	17
3	MTBD (1.0)	toluene	78	5
4	P2-*t*-Bu (1.0)	toluene	62	8
5	KO*t*-Bu (1.0)	toluene	16	23
6	MTBD (1.0)	THF	71	7
7	MTBD (1.0)	1,4-dioxane	69	9
8	MTBD (1.0)	DME	57	19
9	MTBD (1.0)	MeCN	85	5
10	MTBD (1.0)	DMF	77	3
11	MTBD (1.0)	CH_2Cl_2	55	28
12[c]	MTBD (0.20)	MeCN	90 (89)[d]	5
13[e]	MTBD (0.10)	MeCN	82	3

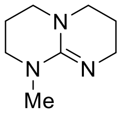
[a] The solution of base and *p*-toluidine **2a** (0.055 mol, 1.1 equiv.) in dry solvent (1.0 mL) were added to the solution of **1a** (0.050 mmol) in dry solvent (1.0 mL) under an argon atmosphere. [b] Yields determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard. [c] For 30 min. [d] Value in the parenthesis is isolated yield. [e] For 40 min.



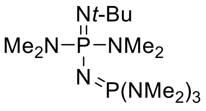
DBU



TMG



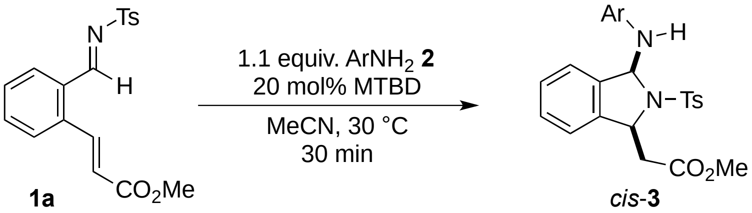
MTBD



P2-*t*-Bu

After the optimal reaction conditions were identified, the influence of various aniline derivatives in the desired product yield was investigated (Table 2). The reactions proceeded efficiently using aniline **2b**, *p*-anisidine **2c**, 4-chloroaniline **2d**, and 4-bromoaniline **2e** affording the corresponding products *cis*-**3ab**–**3ae** in 82%–91% yield (entries 2–5). However, the reaction using 4-nitroaniline **2f** resulted in a diminished yield (63%) because of the instability of *cis*-**3af** (entry 6). Based on the results of the reactions with various aniline derivatives, aminalization/IMAMR of **1a** with **2c** was performed on a larger scale. Thus, with 171.7 mg (0.50 mmol) of **1a**, *cis*-**3ac** was obtained in comparable yield (89%) (entries 3 and 7).

Table 2. Scope of Anilines **2**[a]

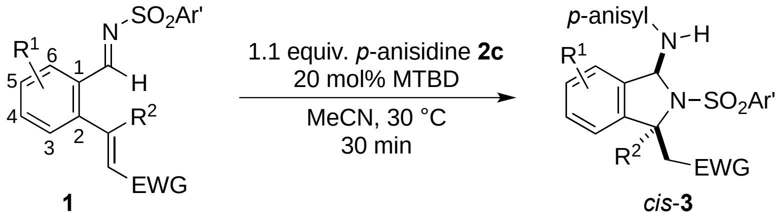


Entry	2	Ar	*cis*-3	Yield/%[b]
1	**2a**	*p*-tol	**3aa**	89
2	**2b**	Ph	**3ab**	83
3	**2c**	*p*-anisyl	**3ac**	91
4	**2d**	4-ClC_6H_4	**3ad**	86
5	**2e**	4-BrC_6H_4	**3ae**	82
6	**2f**	4-$NO_2C_6H_4$	**3af**	63
7[c]	**2c**	*p*-anisyl	**3ac**	89

[a] The solution of MTBD (0.010 mmol, 20 mol%) and aniline derivatives **2** (0.055 mol, 1.1 equiv.) in dry MeCN (1.0 mL) were added to the solution of **1a** (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere. [b] Isolated yields. [c] The reaction was performed on a 0.50 mmol scale.

The application scope of the cascade process was further investigated using a series of *N*-protected imines **1** and *p*-anisidine **2c** (Table 3). α,β-Unsaturated esters (**1b** and **1d**) and nitrile (**1e**) are excellent substrates for producing the corresponding desired products *cis*-**3bc**, *cis*-**3dc**, and *cis*-**3ec** in 90%–93% yield (entries 1, 3, and 4). However, the use of **1c** bearing a bulky *tert*-butyl ester group resulted in a diminished yield of *cis*-**3cc** because of the formation of the corresponding exchanged-imine derived from **1c** and **2c** (entry 2). The imines with an electron-donating group (**1f**) and an electron-withdrawing group (**1g**) on the benzene unit were tolerated, affording the corresponding products *cis*-**3fc** and *cis*-**3gc** in 84% and 90% yield, respectively (entries 5 and 6). In the case of **1h** with a β-methyl substituent in the α,β-unsaturated ester moiety, the desired cascade process was completely suppressed (entry 7). The reaction of a series of imines bearing benzenesulfonyl (**1i**), *p*-anisolesulfonyl (**1j**), and 4-chlorobenzenesulfonyl (**1k**) groups produced *cis*-**3ic**, *cis*-**3jc**, and *cis*-**3kc** in 52%–91% yield, respectively (entries 8–10).

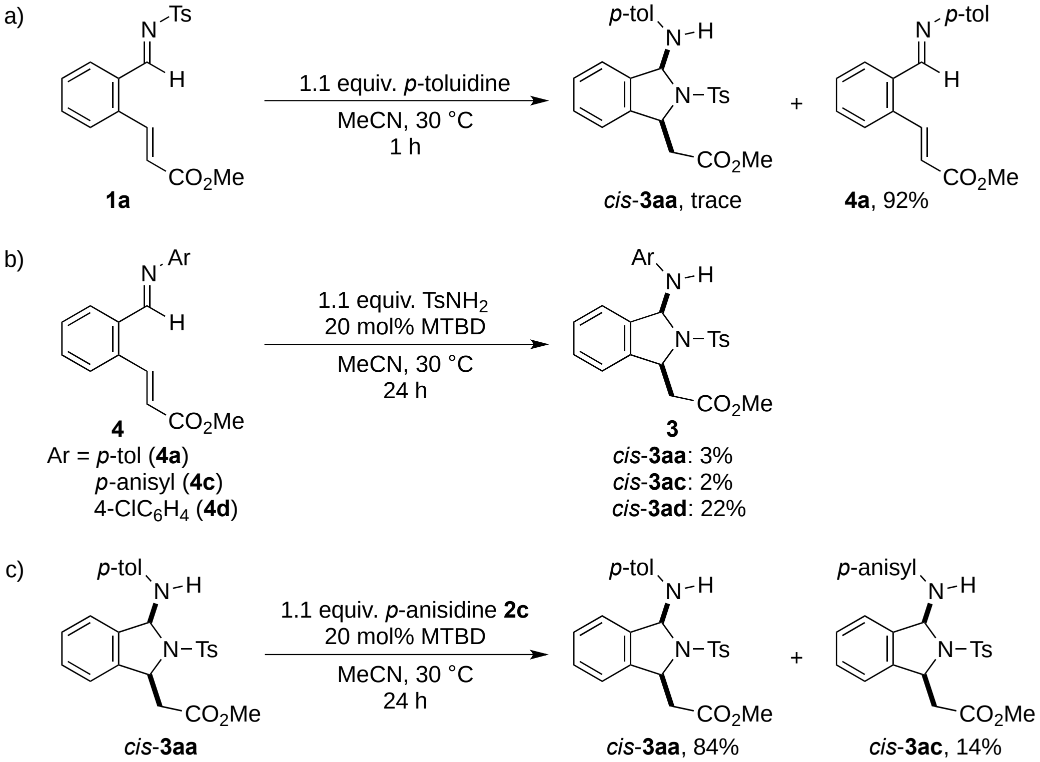
Table 3. Scope of Imines **1**[a]



Entry	**1**	EWG	R^1	R^2	Ar'	*cis*-**3**	Yield/%[b]
1	**1b**	CO_2Et	H	H	*p*-tol	**3bc**	90
2	**1c**	CO_2*t*-Bu	H	H	*p*-tol	**3cc**	44
3	**1d**	CO_2Bn	H	H	*p*-tol	**3dc**	92
4	**1e**	CN	H	H	*p*-tol	**3ec**	93
5	**1f**	CO_2Me	4-MeO	H	*p*-tol	**3fc**	84
6	**1g**	CO_2Me	5-Cl	H	*p*-tol	**3gc**	90
7	**1h**	CO_2Me	H	Me	*p*-tol	**3hc**	n.d.[c]
8	**1i**	CO_2Me	H	H	Ph	**3ic**	87
9	**1j**	CO_2Me	H	H	*p*-anisyl	**3jc**	91
10	**1k**	CO_2Me	H	H	4-ClC_6H_4	**3kc**	52

[a] The solution of MTBD (0.010 mmol, 20mol%) and *p*-anisidine **2c** (0.055 mol, 1.1 equiv.) in dry MeCN (1.0 mL) were added to the solution of **1** (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere.
[b] Isolated yields. [c] Not determined due to the exclusive formation of exchanged-imine derived from **1h** and **2c**.

On the basis of the position of the arylamino group in all the corresponding *cis*-**3** products, the cascade reaction seems to be initiated by aminalization of imine **1** with aniline **2** (Table 1–3). To gain more insight into this cascade reaction, several control reactions were conducted (Scheme 2). In the absence of MTBD, the exchanged-imine **4a** was formed, exclusively (Scheme 2a). This result suggested that the base catalysts are necessary for the desired cascade process to proceed smoothly. In order to understand the role of exchanged-imine **4** in the cascade process, the reactions were performed with the independently synthesized **4a**, **4c**, or **4d** and *p*-toluenesulfonamide under the optimized conditions (Scheme 2b). These reactions were very sluggish, indicating the formation of *cis*-**3** via a direct route without the formation of imine **4**. Furthermore, the reaction of *cis*-**3aa** with *p*-anisidine **2c** under the optimized conditions resulted in aminal exchange to afford the product *cis*-**3ac** in 14% yield (Scheme 2c). This result indicated that the aminal exchange of **3** occurs under the optimal reaction conditions although the rate of this exchange reaction is very slow.[9,10]



Scheme 2. Experiments for Mechanistic Study

In conclusion, we have developed a catalytic and diastereoselective method for the construction of *cis*-1,3-disubstituted isoindoline skeletons via aminalization and the subsequent intramolecular aza-Michael reaction of *N*-protected imines bearing a Michael acceptor using anilines as nitrogenous nucleophiles. In addition to the aryl sulfonamides used in our previous studies, the cascade process was found to proceed well with the aniline derivatives. Furthermore, MTBD proved to be an excellent base catalyst for this cascade process. The synthetic methods described in our study may be useful in the fields of organic and medicinal chemistry as it provides moderate to high yield of *cis*-1,3-disubstituted isoindolines with aniline-derived aminal functionality.

EXPERIMENTAL

Typical procedure for the preparation of *cis*-1,3-disubstituted isoindolines 3. (1*S,3*S**)-Methyl 2-{3-(4-methylphenylamino)-2-tosylisoindolin-1-yl}acetate (3aa).** To a solution of imine (**1a**; 17.2 mg, 0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of MTBD (1.5 μL, 0.010 mmol, 20 mol%) and *p*-toluidine (**2a**; 6.8 mg, 0.055 mmol, 1.1 equiv.) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 30 min. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography on silica gel (hexane/$CHCl_3$/EtOAc = 6/6/1) to afford *cis*-1,3-disubstituted isoindoline (**3aa**; 20.0 mg, 0.044 mmol, 89%) as pale yellow foam; ^{1}H NMR

(500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.35 (s, 3H), 2.43 (dd, J = 7.7, 16.8 Hz, 1H), 2.93 (dd, J = 3.7, 16.8 Hz, 1H), 3.64 (s, 3H), 4.65 (brs, 1H, N*H*), 5.11 (dd, J = 3.6, 7.7 Hz, 1H), 6.31 (s, 1H), 6.57 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.11–7.13 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.28–7.32 (m, 2H), 7.39–7.41 (m, 1H), 7.72 (d, J = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 20.5 (CH_3), 21.5 (CH_3), 41.4 (CH_2), 51.7 (CH_3), 60.0 (CH), 78.1 (CH), 119.1 (CH), 122.6 (CH), 124.2 (CH), 127.4 (CH), 128.5 (CH), 129.3 (CH), 129.4 (CH), 129.8 (CH), 130.4 (C), 135.3 (C), 137.8 (C), 139.1 (C), 141.9 (C), 143.7 (C), 171.5 (C); IR (KBr) ν: 3385, 3028, 2951, 2917, 2867, 1735, 1520, 1344, 1300, 1163, 1011, 814 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{26}N_2NaO_4S$ 473.1505; Found 473.1508.

Experimental procedures, characterization data, and copies of NMR spectra for all new compounds are available in the Supporting Information.

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REFERENCES AND NOTES

1. For relevant reviews: (a) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; (b) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (c) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (d) C. M. R. Volla, I. Atodiresei, and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (e) F. Vetica, R. M. de Figueiredo, M. Orsini, D. Tofani, and T. Gasperi, *Synthesis*, 2015, **47**, 2139; (f) H. Pellissier, *Synthesis*, 2020, **52**, 3837; (g) N. Losada-Garcia, Z. Cabrera, P. Urrutia, C. Garcia-Sanz, A. Andreu, and J. M. Palomo, *Catalysts*, 2020, **10**, 1258; (h) S. Takizawa, *Chem. Pharm. Bull.*, 2020, **68**, 299.
2. Synthesis of 1,3-disubstituted isoindolines by cascade or domino process: (a) D. Enders, A. A. Narine, F. Toulgoat, and T. Bisschops, *Angew. Chem. Int. Ed.*, 2008, **47**, 5661; (b) S. Fustero, J. Moscardó, M. Sánchez-Roselló, E. Rodríguez, and P. Barrio, *Org. Lett.*, 2010, **12**, 5494; (c) B. Qian, S. Guo, C. Xia, and H. Huang, *Adv. Synth. Catal.*, 2010, **352**, 3195; (d) S. Takizawa, N. Inoue, S. Hirata, and H. Sasai, *Angew. Chem. Int. Ed.*, 2010, **49**, 9725; (e) E. E. Maciver, P. C. Knipe, A. P. Cridland, A. L. Thompson, and M. D. Smith, *Chem. Sci.*, 2012, **3**, 537; (f) S. Takizawa, M. Sako, M. A. Abozeid, K. Kishi, H. D. P. Wathsala, S. Hirata, K. Murai, H. Fujioka, and H. Sasai, *Org. Lett.*, 2017, **19**, 5426; (g) B. G. Das, S. Shah, and V. K. Singh, *Org. Lett.*, 2019, **21**, 4981; (h) Z.-R. Guan, Q. Wan, and M.-W. Ding, *Tetrahedron*, 2019, **75**, 4626; (i) K. Hirano, T. Saito, Y. Fujihira, D. M. Sedgwick, S. Fustero, and N. Shibata, *J. Org. Chem.*, 2020, **85**, 7976.

3. Selected recent reports on the synthesis of 1,3-disubstituted isoindolines: (a) S. Xing, J. Ren, K. Wang, H. Cui, H. Yan, and W. Li, *Adv. Synth. Catal.*, 2016, **358**, 532; (b) R. Achary, I.-A. Jung, S.-M. Son, and H.-K. Lee, *J. Org. Chem.*, 2017, **82**, 7223; (c) R. Achary, I.-A. Jung, and H.-K. Lee, *J. Org. Chem.*, 2018, **83**, 3864; (d) Y. Tao and S. R. Gilbertson, *Chem. Commun.*, 2018, **54**, 11292; (e) S. Xing, H. Cui, J. Qin, N. Gu, B. Zhang, K. Wang, Y. Wang, L. Xia, and Y. Wang, *Org. Chem. Front.*, 2018, **5**, 1950; (f) Z. Feng, Z. Yuan, X. Zhao, Y. Huang, and H. Yao, *Org. Chem. Front.*, 2019, **6**, 3535 and references cited therein.
4. Selected review and reports: (a) K. Speck and T. Magauer, *Beilstein J. Org. Chem.*, 2013, **9**, 2048; (b) M. S. Leonard, *ARKIVOC*, 2013, **i**, 1; (c) J. L. Moniot, D. M. Hindenlang, and M. Shamma, *J. Org. Chem.*, 1979, **44**, 4347; (d) M. Goldstein, S. Kuga, N. Kusano, E. Meller, J. Dancis, and R. Schwarcz, *Brain Res.*, 1986, **367**, 114; (e) A. L. Jaton, R. K. A. Giger, J. M. Vigouret, A. Enz, W. Frick, A. Closse, and R. Markstein, *Life Sci.*, 1986, **38**, 155; (f) Z. Hussein, D. J. Mulford, B. A. Bopp, and G. R. Granneman, *Br. J. Clin. Pharmacol.*, 1993, **36**, 357; (g) T. Kondo, K. Yoshida, and S. Tanayama, *Arzneimittelforschung*, 1996, **46**, 839; (h) P. J. Kukkola, N. A. Bilci, T. Ikler, P. Savage, S. S. Shetty, D. DelGrande, and A. Y. Jeng, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1737; (i) T. L. Stuk, B. K. Assink, R. C. Bates, D. T. Erdman, V. Fedij, S. M. Jennings, J. A. Lassig, R. J. Smith, and T. L. Smith, *Org. Process Res. Dev.*, 2003, **7**, 851.
5. T, Tsujihara, H. Yamauchi, S. Tamura, T. Takehara, T. Suzuki, and T. Kawano, *Tetrahedron Lett.*, 2020, **61**, 152122.
6. I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito, and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019.
7. As previously reported regarding the structure of *cis*-form (ref. 5), the substituents at the 1 and 3 positions should be located *anti* to the *p*-toluenesulfonyl group on the nitrogen. Therefore, the *cis*-isomer of **3** was formed to avoid steric repulsion between each substituent on the isoindoline skeleton.
8. For the determination of the structure of *cis*-**3aa** in detail, see the Supporting Information.
9. The aminal exchange of *cis*-**3** might have proceeded through a *retro*-Michael reaction or the formation of an *N*-sulfonyliminium cation. See the supporting information for the plausible reaction mechanisms of aminal exchange (Scheme S1).
10. As the intramolecular aza-Michael process is reversible, *cis*-**3**, which is thermodynamically more stable than the *trans*-form, should be produced as a single diastereomer. (a) T. Kurihara, K. Fukunaga, T. Sakaguchi, and H. Hirano, *J. Heterocycl. Chem.*, 1975, **12**, 989; (b) P. Sanaa, F. Savelli, and G. Cignarella, *J. Heterocycl. Chem.*, 1981, **18**, 475; (c) P. J. Kukkola, N. A. Bilci, and T. J. Ikeler, *Tetrahedron Lett.*, 1996, **37**, 5065. See also Scheme S2 in the Supporting Information.