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Synthesis of Optically Active 2,3-Disubstituted Indoline Derivatives through Cycloaddition Reactions between Benzynes and α,β-Unsaturated γ-Aminobutyronitriles

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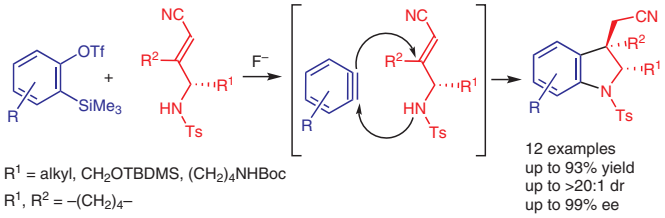

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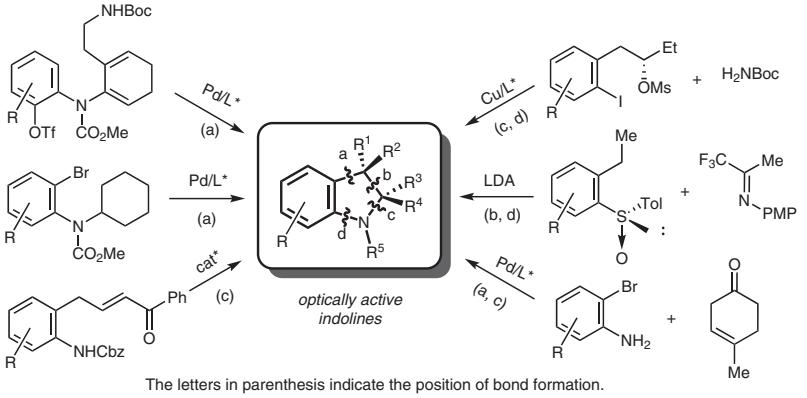
Abstract We report a method for synthesizing optically active 2,3-disubstituted indolines by the cycloaddition reaction of benzynes with various 4-[(4-toluenesulfonyl)amino]-(*E*)-but-2-enenitriles, which are readily prepared from the corresponding L-amino acid derivatives.

Keywords indolines, benzynes, cycloaddition, asymmetric synthesis, nucleophilic addition, amino acids

The indoline framework is one of the most important skeletons present in biologically active natural products.[1] Currently, two general approaches exist for the synthesis of indolines. The first of these methods is based on the dearomatization of indoles by polyfunctionalization of the C2–C3 double bond.[2] This type of strategy has been applied to a number of stereoselective syntheses of complex natural products; however, it requires the corresponding indoles to be prepared in advance.[3] The second route to the indoline framework is based on the construction of the pyrrolidine ring through C–C bond formation at the (a) or (b) bonds or C–N bond formation at the (c) or (d) bonds (Scheme 1).[4] However, only a few methods have been reported for the direct enantio- and diastereoselective construction of the C2 and C3 stereogenic centers of substituted indolines without the need for prior synthesis of the indole moiety. Consequently, the development of a novel synthetic route to optically active indolines by using an alternative stereoselective cyclization approach is of particular interest.

In this context, many reactions of benzynes with novel arynophiles have been reported in the past few decades.[5] One particular benefit of such reactions is the simultaneous formation of two sigma bonds at adjacent positions of a benzene ring,[5] so that these efficient transformations have the potential to render molecular syntheses more concise and attractive. Despite such advances, examples of stereoselective bond-forming reactions involving benzyne are limited.[6] Here, we present novel syntheses of optically active 2,3-disubstituted indolines **1** through a cycloaddition protocol between benzynes **2** and optically active (*E*)-4-aminobut-2-enenitriles **3**,[7–9] which are readily available



Scheme 1 Reported syntheses of the indoline framework based on cyclization reactions.

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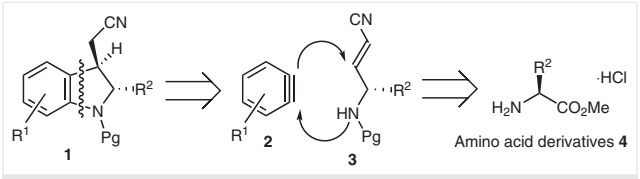
through a three-step telescoping process from commercially available L-amino acid methyl ester derivatives **4** (Scheme 2).

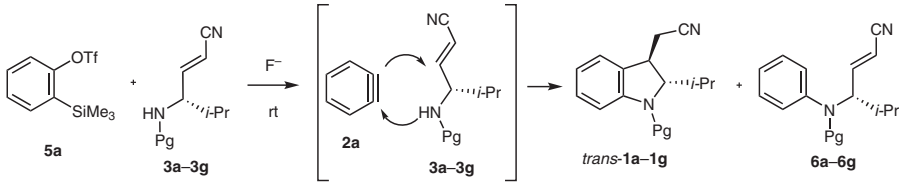
We initially examined the feasibility of the cycloaddition protocol by generating benzyne (**2a**, R^1 = H) from 2-(trimethylsilyl)phenyl triflate (**5a**, R^1 = H; 1.0 equiv) and CsF (2.0 equiv), and reacting it with (2*E*,4*S*)-4-benzylamino-5-methylhex-2-enenitrile (**3a**, R^2 = *i*-Pr; R^3 = H; Pg = Bn; 1.5 equiv), a process that involves the nucleophilic addition of the amino group of **3a** to **2a**, and subsequent intramolecular Michael addition to the α,β-unsaturated nitrile moiety to produce indoline **1a** (Pg = Bn) (Table 1). The reaction in MeCN at room temperature for one hour produced **1a** in 47% isolated yield with good diastereoselectivity (dr = 6.7:1), with the *trans*-product being the major isomer (Table 1, entry 1). A single-addition product **6a** (41%)[10] was also produced in this reaction. However, the application of these reaction conditions to nitriles **3** (R^2 = *i*-Pr; R^3 = H) bearing various protecting groups [Pg = Boc (**3b**), Ac (**3c**), 4-$O_2NC_6H_4SO_2$ (Ns) (**3d**), Ms (**3e**), Ts (**3f**)] produced significantly different results. More specifically, neither the addition product **6** nor the cycloaddition product **1** were formed from **3b** bearing a *tert*-butoxycarbonyl (Boc) group or from **3c** bearing an Ac group (entries 2 and 3). In contrast, nitriles



Scheme 2 Strategy for the stereoselective syntheses of indolines through cycloaddition reactions of benzynes

3d–f bearing sulfonyl-type protecting groups gave **1** with high diastereoselectivities (dr = >20:1) and in 32–54% yields (entries 4–6).[11,12] The use of alternative solvents or other fluoride sources, such as KF/18-crown-6 (18-c-6) or tetrabutylammonium difluorotriphenylsilicate (TBAT), produced varied yields of the cycloaddition product **1f** and addition product **6f**, in addition to giving good diastereomeric ratios of **1f** (entries 7–13). The optimal yield of **1f** (71%) was obtained in the presence of CsF and 18-c-6 in THF at room temperature (entry 10). The reaction carried out at a lower temperature (−40 °C) gave a similar result (entry 11). Furthermore, the presence of larger protecting groups (Pg = SO_2Mes; **3g**) lowered the diastereoselectivity of **1g** (dr = 6.9:1, entry 14).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Pg	F^- source	Solvent	Reactant	Products	Yield of **1** (%)[b]	Yield of **6** (%)[b]	dr[c]
1	Bn	CsF	MeCN	**3a**	**1a**, **6a**	47	41	6.7:1
2	Boc	CsF	MeCN	**3b**	**1b**, **6b**	nd[d]	nd[d]	–
3	Ac	CsF	MeCN	**3c**	**1c**, **6c**	nd[d]	nd[d]	–
4	Ns	CsF	MeCN	**3d**	**1d**, **6d**	54	32	19:1
5	Ms	CsF	MeCN	**3e**	**1e**, **6e**	32	30	15:1
6	Ts	CsF	MeCN	**3f**	**1f**, **6f**	44	36	>20:1
7	Ts	CsF/18-crown-6	MeCN	**3f**	**1f**, **6f**	54	37	12:1
8	Ts	KF/18-crown-6	MeCN	**3f**	**1f**, **6f**	55	36	13:1
9	Ts	TBAT	MeCN	**3f**	**1f**, **6f**	19	13	–
10	Ts	CsF/18-crown-6	THF	**3f**	**1f**, **6f**	71	22	16:1
11[e]	Ts	CsF/18-crown-6	THF	**3f**	**1f**, **6f**	69	15	17:1
12	Ts	KF/18-crown-6	THF	**3f**	**1f**, **6f**	50	16	>20:1
13	Ts	TBAT	THF	**3f**	**1f**, **6f**	48	12	>20:1
14	SO_2Mes	CsF/18-crown-6	THF	**3g**	**1g**, **6g**	69	20	6.9:1

[a] Reaction conditions: **5a** (1.0 equiv), **3** (1.5 equiv), F^- source (3.0 equiv), solvent (0.05 M), r.t., 1.0 h.
[b] Determined by ^{1}H NMR analysis with DMF as the internal standard.
[c] dr = ratio of *trans*- and *cis*-diastereomers of **1**.
[d] nd = not detected.
[e] Conducted at −40 °C.

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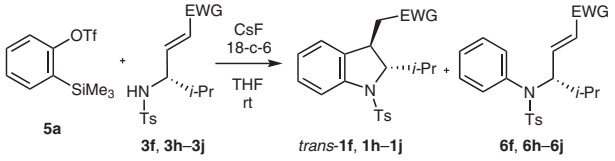
We also found that the optically pure α,β-unsaturated nitrile **3f** was the most suitable for production of the optically pure indoline **1f** (R^2 = *i*-Pr; R^3 = H; 75% isolated yield, *trans*/*cis* = 18:1, 99% ee of *trans*-**1f**) (Table 2, entry 1). Similar reactions also proceeded with the corresponding γ-amino α,β-unsaturated ester **3h** (EWG = CO_2Me; entry 2) and ketone **3i** (EWG = COMe; entry 3), but with lower optical purities (95% ee for **1h** and 84% ee for **1i**). These differences were probably caused by changes in the optical purities of **3h** and **3i** under the reaction conditions employed. Indeed, although the optical purity of **3f** remained >99% ee under these reaction conditions after 12 hours, those of **3h** (98% ee) and **3i** (96% ee) decreased significantly to 68% and 48% ee, respectively, and unidentified decomposition products were observed (see Supporting Information). These results indicate that the appropriate electron-withdrawing ability of the cyano group determined the optical integrity and reactivity of **3**, whereas the more-strongly electron-withdrawing ester and keto groups caused partial racemization. Furthermore, the reaction carried out by using the nitro substrate **3j** (EWG = NO_2) gave indoline **1j** with a lower yield of 64%, probably due to the instability of **3j** under the basic reaction conditions (entry 4).

Table 2 Effects of Varying the Electron-Withdrawing Group[a]

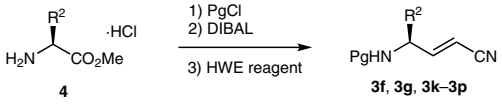


Entry	EWG (**3**)	Yield of **1** (%)[b]	Yield of **6** (%)[b]	dr[c]	ee (%)[d]
1	CN (**3f**)	75 (**1f**)	20 (**6f**)	18:1	>99
2	CO_2Me (**3h**)	75 (**1h**)	6 (**6h**)	17:1	94
3	COMe (**3i**)	79 (**1i**)	10 (**6i**)	12:1	84
4	NO_2 (**3j**)	64 (**1j**)	19 (**6j**)	15:1	–

[a] Reaction conditions: **5a** (1.5 equiv), **3** (1.0 equiv), CsF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (0.05 M), r.t., 1.0 h.
[b] Determined by ^{1}H NMR analysis with DMF as the internal standard.
[c] dr = ratio of *trans*- and *cis*-diastereomers **1**.
[d] ee = enantiomeric excess of the major diastereomer *trans*-**1**.

An efficient three-step telescoping synthesis[13] of various γ-amino α,β-unsaturated nitriles **3** from commercially available L-amino acid methyl esters **4** is shown in Table 3. After protection of the amino groups of **4**, the resulting esters were reduced by using DIBAL-H to give the corresponding aldehydes, and the resulting mixtures were subjected to reaction with the Horner–Wadsworth–Emmons (HWE) reagent [$NCCH_2PO(OEt)_2$] to produce γ-amino a, b-unsaturated nitriles **3f**, **3g**, and **3k–p** in good to moderate overall yields (30–82%) without isolation between the various steps. It is worth noting that the chiral integrity of L-valine (**4a**) as a starting amino acid was maintained under these reaction conditions, yielding **3f** in an excellent enantiomeric excess of >99% (entry 1).[14]

Table 3 Telescoping Synthesis of γ-Amino α,β-Unsaturated Nitriles **3** from Amino Acids **4**[a]



Entry	Reactant	R^2	Pg	Product	Yield (%)[b]
1	**4a**	*i*-Pr	Ts	**3f**	63[c]
2	**4a**	*i*-Pr	SO_2Mes	**3g**	55
3	**4b**	Me	Ts	**3k**	36
4	**4c**	Bn	Ts	**3l**	82
5	**4d**	*i*-Bu	Ts	**3m**	67
6	**4d**	*i*-Bu	Ns	**3n**	55
7	**4e**	CH_2OH	Ts	**3o′**	30[d]
8	**4f**	$(CH_2)_4NHBoc$	Ts	**3p**	69[e]

[a] Reaction conditions: (1) **4** (1.0 equiv), PgCl (1.2 equiv), Et_3N (2.5 equiv), CH_2Cl_2 (0.50 M), r.t.; (2) DIBAL (2.5 equiv), CH_2Cl_2 (0.50 M), −80 °C, 2 h; (3) $NCCH_2PO(OEt)_2$ (1.0 equiv), DIPEA (1.0 equiv), LiCl (1.5 equiv), MeCN (0.20 M), r.t.
[b] Isolated yield.
[c] >99% ee.
[d] Silylation was conducted by using TBDMSCl following the tosylation of **4e**.
[e] Synthesized from commercial Fmoc-Lys(Boc)-OH in five steps.

We then applied the optimized reaction conditions to a range of γ-amino α,β-unsaturated nitriles **3k–p** (Table 4). In all cases, the corresponding indolines **1** were obtained in good to moderate yields. Although less-bulky R^2 substituents such as Me (Table 4, entries 1 and 2), Bn (entry 3), *i*-Bu (entries 4 and 5), $CH_2OTBDMS$ (entries 8 and 9), CH_2OH (entry 10), or $(CH_2)_4NHBoc$ (entry 11) rendered the reaction less diastereoselective (c.f., *i*-Pr; Table 2, entry 1), higher selectivities were observed at lower temperatures (−40 °C; entries 2, 7, and 9). Under these conditions, silyloxy (entry 9), hydroxy (entry 10), and *N*-Boc functional groups (entry 11) were also tolerated. In addition, when Ns was employed as an amine-protecting group instead of Ts, a lower yield was obtained (c.f., **1n** and **1m**, entries 4–7). It should also be noted that the reaction of **3f** with 3-methoxybenzyne (**2b**) (R^1 = OMe, entry 12)[15] and with 3-TBDMS-benzyne **2c** (R^1 = TBDMS, entry 13)[16] provided the desired products **1q** and **1r** with excellent regioselectivities. In these transformations, the initial addition of the amino group took place at the position *meta* to the OMe and silyl groups.

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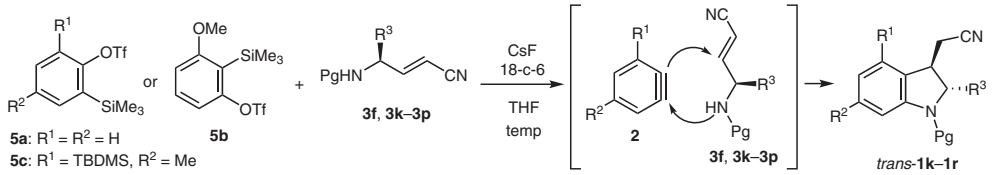
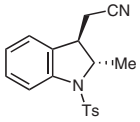
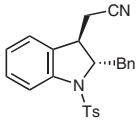
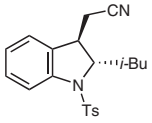
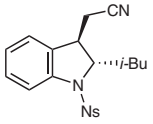
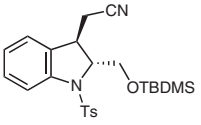
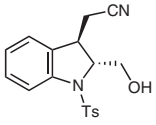
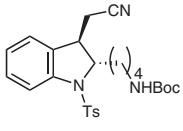
Table 4 Substrate Scope of the Reaction[a]



Entry	Reactants	Benzyne	Temp (°C)	Product	1	Yield (%)[b]	dr[c,d]
1	**5a**, **3k**	 **2a**	r.t.		*trans*-**1k**	19	1.1:1
2	**5a**, **3k**		–40			76	2.3:1
3	**5a**, **3l**	**2a**	r.t.		*trans*-**1l**	93	5.0:1
4	**5a**, **3m**	**2a**	r.t.		*trans*-**1m**	73	2.3:1
5	**5a**, **3m**		–40			72	2.4:1
6	**5a**, **3n**	**2a**	0		*trans*-**1n**	58	4.2:1
7	**5a**, **3n**		–40			24	4.8:1
8	**5a**, **3o'**	**2a**	r.t.		*trans*-**1o'**	70	2.5:1
9			–40			65	4.0:1
10	**5a**, **3o**	**2a**	–40		*trans*-**1o**	57	2.4:1
11	**5a**, **3p**	**2a**	–40		*trans*-**1p**	63	3.5:1

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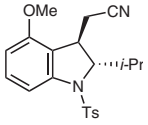
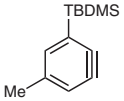
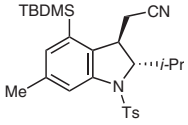
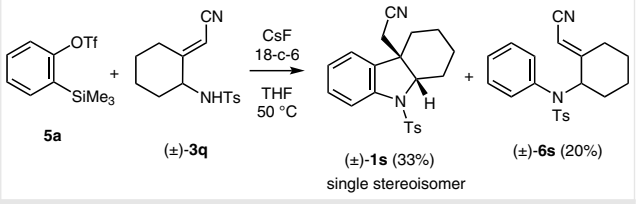
Entry	Reactants	Benzyne	Temp (°C)	Product	1	Yield (%)[b]	dr[c,d]
12	**5b**, **3f**	 **2b**	–40		*trans*-**1q**	72	>20:1
13	**5c**, **3f**	 **2c**	r.t.		*trans*-**1r**	68	>20:1

[a] Conditions: **5** (1.5 equiv), **3** (1.0 equiv), CsF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (0.05 M), 1 h.
[b] Isolated yield.
[c] dr = ratio of *trans*- and *cis*-diastereomers **1**.
[d] Determined by ^{1}H NMR measurements.

As outlined in Scheme 3, the hexahydrocarbazole **1s** was also synthesized by this method. More specifically, the reaction of **5a** with cyclic tosylamide (±)-**3q** provided (±)-**1s** (33%) with high diastereoselectivity[17] at 50 °C, although a lower yield was obtained than when the acyclic substrates **3** were employed, due to the formation of a significant amount (20%) of the monoaddition product **6s**.



Scheme 3 Synthesis of hexahydrocarbazole (±)-**1s** from cyclic tosylamide (±)-**3q**

In summary, we successfully developed a synthesis of optically active 2,3-disubstituted indolines through cycloaddition reactions between benzynes and γ-amino α,β-unsaturated nitriles,[18–20] in which the use of a cyano group as the electron-withdrawing group gave superior results to the use of an ester[8a] or carbonyl group, resulting in retention of the optical integrity of the arynophile. This method is of particular importance in the area of synthetic chemistry, as the nitrile group of the indoline products can be transformed into a range of other functional groups. As such, our protocol opens a potential new route that permits synthetic and/or medicinal chemists to prepare biologically active compounds bearing the indoline moieties. Studies on applications of this transformation and detailed mechanistic investigations are now underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591722.

References and Notes

(1) For biologically active indoline papers, see: (a) Bechle, B. M.; Didiuk, M. T.; Fritzen, E. L.; Garigipati, R. S. WO 2006032987, **2006**. (b) Goodman, F. R.; Weiss, G. B.; Hurley, M. E. *Cardiovasc. Drug Rev.* **1985**, *3*, 57. (c) Poondra, R. R.; Kumar, N. N.; Bijian, K.; Prakesch, M.; Campagna-Slater, V.; Reayi, A.; Reddy, P. T.; Choudhry, A.; Barnes, M. L.; Leek, D. M.; Daroszewska, M.; Lougheed, C.; Xu, B.; Schapira, M.; Alaoui-Jamali, M. A.; Arya, P. *J. Comb. Chem.* **2009**, *11*, 303. (d) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1366. (e) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966. (f) Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. *J. Clin. Pharmacol.* **1986**, *26*, 156. (g) Xiang, L.; Xing, D.; Wang, W.; Wang, R.; Ding, Y.; Du, L. *Phytochemistry* **2005**, *66*, 2595. (h) Yang, Z.; Liu, C.; Xiang, L.; Zheng, Y. *Phytother. Res.* **2009**, *23*, 1032.

(2) For selected reviews on syntheses of indolines by dearomatization of indoles, see: (a) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (b) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.*

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2015, *48*, 702. For selected papers on indoline syntheses by dearomatization reactions, see. (c) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614. (d) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8809. (e) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (f) Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883. (g) Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596. (h) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (i) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57. (j) Awata, A.; Arai, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 10462.

(3) For selected reviews on indole synthesis, see: (a) Wu, H.; He, Y.-P.; Shi, F. *Synthesis* **2015**, *47*, 1990. (b) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702. (c) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (d) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160.

(4) For reviews on syntheses of indolines through the formation of pyrrolidine rings, see: (a) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193. (b) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975. For selected papers, see: (c) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186. (d) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7438. (e) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658. (f) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (g) Ruano, J. L. G.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7941. (h) Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177. (i) Pian, J.-X.; He, L.; Du, G.-F.; Guo, H.; Dai, B. *J. Org. Chem.* **2014**, *79*, 5820.

(5) For selected recent reviews on benzynes, see: (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (b) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987. (c) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (e) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (f) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (g) Yoshida, H. In *Comprehensive Organic Synthesis II*; Knochel, P.; Molander, G. A., Eds.; Elsevier: Amsterdam, **2014**, 517. (h) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450. (i) Karmakar, R.; Lee, D. *Chem. Soc. Rev.* **2016**, *45*, 4459. (j) Zeng, Y.; Hu, J. *Synthesis* **2016**, *48*, 2137.

(6) For stereoselective benzyne reactions, see: (a) Webster, R.; Lautens, M. *Org. Lett.* **2009**, *11*, 4688. (b) Peña, D.; Pérez, D.; Guitián, E. *Chem. Rec.* **2007**, *7*, 326. (c) Caeiro, J.; Peña, D.; Cobas, A.; Párez, D.; Guitián, E. *Adv. Synth. Catal.* **2006**, *348*, 2466. (d) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028.

(7) For indoline syntheses through reactions with benzynes, see: (a) Guo, J.; Kiran, C. I. N.; Gao, J.; Reddy, R. S.; He, Y. *Tetrahedron Lett.* **2016**, *57*, 3481. (b) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

(8) During the preparation of this manuscript (see Ref. 9), closely related work was published by the groups of Sudalai and She: (a) Aher, R. D.; Suryavanshi, G. M.; Sudalai, A. *J. Org. Chem.* **2017**, *82*, 5940. (b) Xu, D.; Zhao, Y.; Song, D.; Zhong, Z.; Feng, S.; Xie, X.; Wang, X.; She, X. *Org. Lett.* **2017**, *19*, 3600.

(9) For preliminary work carried out in relation to this study, see: Ikawa, T.; Sumii, Y.; Takagi, A.; Akai, S. *The 135th Annual Meeting of the Pharmaceutical Society of Japan (Kobe, March, 2015), Abstract Book No. 2.* Pharmaceutical Society of Japan: Tokyo: 83

(10) For studies discussing the addition of nitrogen nucleophiles to benzynes, see: (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. (c) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673. (d) Li, L.; Qiu, D.; Shi, J.; Li, Y. *Org. Lett.* **2016**, *18*, 3726.

(11) The use of our newly developed precursor, 2-(trimethylsilyl)phenyl trimethylsilyl ether (see Ref. 12) instead of **5a** also gave *trans*-**1f** (46%, dr = 14:1) and **6f** (39%), which was very similar to Table 1, entry 6. The reaction was performed with the silyl ether (1.5 equiv), nonaflourobutane-1-sulfonyl fluoride (2.3 equiv), **3f** (1.0 equiv), and CsF (4.5 equiv) in MeCN (0.10 M) at 60 °C for 26 h.

(12) Ikawa, T.; Masuda, S.; Nakajima, H.; Akai, S. *J. Org. Chem.* **2017**, *82*, 4242.

(13) For an introduction to telescoping syntheses, see: (a) Nishimura, K.; Saitoh, T. *Chem. Pharm. Bull.* **2016**, *64*, 1043. (b) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, **2000**. (c) Ikemoto, T. In *Process Chemistry of Pharmaceuticals*; Kagaku-Dojin Publishing: Kyoto, **2013**, (in Japanese).

(14) Sudalai and co-workers reported that γ-amino α,β-unsaturated nitriles could not be obtained (see Ref. 8a).

(15) For selected examples related to 3-methoxybenzyne, see: (a) Shi, J.; Qiu, D.; Wang, J.; Xu, H.; Li, Y. *J. Am. Chem. Soc.* **2015**, *137*, 5670. (b) Umezu, S.; dos Passos Gomes, G.; Yoshinaga, T.; Sakae, M.; Matsumoto, K.; Iwata, T.; Alabugin, I.; Shindo, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 1298. (c) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735. (d) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 3247. (e) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(16) For selected recent papers on silylbenzynes, see: (a) Akai, S.; Ikawa, T.; Takayanagi, S.-i.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y.; Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 7673. (b) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613. (c) Diemer, V.; Begaud, M.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2011**, 341. (d) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.-i.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5674. (e) Ikawa, T.; Tokiwa, H.; Akai, S. *J. Synth. Org. Chem., Jpn.* **2012**, *70*, 1123. (f) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966. (g) Ikawa, T.; Takagi, A.; Goto, M.; Aoyama, Y.; Ishikawa, Y.; Itoh, Y.; Fujii, S.; Tokiwa, H.; Akai, S. *J. Org. Chem.* **2013**, *78*, 2965. (h) Yoshida, H.; Yoshida, R.; Takaki, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8629. (i) Ikawa, T.; Urata, H.; Fukumoto, Y.; Sumii, Y.; Nishiyama, T.; Akai, S. *Chem. Eur. J.* **2014**, *20*, 16228. (j) Ikawa, T.; Masuda, S.; Takagi, A.; Akai, S. *Chem. Sci.* **2016**, *7*, 5206.

(17) The corresponding diastereomer of (±)-**1s** was below the detection limit of ^{1}H NMR (>50:1).

(18) **Indolines 1a–r; General Procedure**

A test tube was charged with the appropriate benzyne precursor **5** (1.5 equiv) and a magnetic stir bar. THF (1.0 mL, 50 mM), which did not have to be anhydrous, was added to the tube and the mixture was stirred for a few minutes to dissolve **5**. The γ-tosylamino α,β-unsaturated nitrile **3** (1.0 equiv) and 18-crown-6 (3.0 equiv) were added to the solution, and the flask was equipped with a screw cap. (This solution was stirred for 10 min at the indicated temperature when the reaction was conducted at 0 °C or below.) CsF (3.0 equiv) was quickly added to the test tube, which was then resealed with the screw cap, and the mixture was stirred at the appropriate temperature until either

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the α,β-unsaturated nitrile **3** or the benzyne precursor **5** was consumed (TLC). The mixture was then passed through a short pad of silica gel with elution by EtOAc, and solvents were removed under reduced pressure. The residue was subjected to ^{1}H NMR analysis to determine the ratio of the two diastereomers (*trans*-**1** and *cis*-**1**). The crude product was purified by flash column chromatography (silica gel) or by preparative TLC (hexane–EtOAc, hexane–CH_2Cl_2, or EtOAc) to afford the required substituted indoline **1** and the single-addition product **6**.

(19) **{(2*S*,3*R*)-2-Isopropyl-1-tosyl-2,3-dihydro-1*H*-indol-3-yl}acetonitrile (*trans*-1f)**

According to the general procedure, a mixture of CsF (91 mg, 0.60 mmol), 18-crown-6 (0.16 g, 0.60 mmol), triflate **5a** (90 mg, 0.30 mmol), and sulfonamide **3f** (56 mg, 0.20 mmol) was stirred in THF (2.0 mL, 0.10 M) for 1 h at r.t. The crude product (*trans*-**1f**/*cis*-**1f** = 16:1, determined by 400 MHz ^{1}H NMR analysis) was purified by column chromatography [silica gel, hexane–EtOAc (20:1 to 4:1)] to give a colorless solid; yield: 51 mg (72%, >99% ee); mp 139–141 °C; $[\alpha]_D^{25}$ –137.4 (*c* 0.12, $CHCl_3$).

The relative stereochemistry was determined by NOESY spectroscopy, and the optical purity was determined by HPLC. HPLC: CHIRALCEL AD-3 [hexane–*i*-PrOH (80:20), 1.0 mL/min, 20 °C]; t_r = 12.7 min (2*S*,3*R*), 9.1 min (2*R*,3*S*). IR (neat): 3446, 2964, 2251, 1597 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H), 1.11 (dd, *J* = 17.0, 9.5 Hz, 1 H), 1.68 (dd, *J* = 17.0, 7.0 Hz, 1 H), 2.15 (sept d, *J* = 7.0, 5.0 Hz, 1 H), 2.36 (s, 3 H), 3.05–3.09 (m, 1 H), 3.77 (dd, *J* = 5.0, 2.0 Hz, 1 H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.32 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 18.1, 21.5, 24.0, 33.3, 39.2, 72.1, 117.3, 117.5, 124.5, 125.1, 127.0, 129.5, 129.8, 132.9, 134.6, 141.6, 144.5. HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_2NaO_2S$: 377.1294; found: 377.1291.

All spectroscopic data for product (2*S*,3*R*)-**1f** were in good agreement with those for (±)-*trans*-**1f**, synthesized from (±)-**3f**.

(20) **{(2*S*,3*S*)-2-Isopropyl-1-tosyl-2,3-dihydro-1*H*-indol-3-yl}acetonitrile (*cis*-1f)**

Obtained from above-mentioned crude reaction mixture as a colorless solid; yield: 2.4 mg (3%); mp 131–133 °C; $[\alpha]_D^{20}$ –2.4 (*c* 0.12, $CHCl_3$). The relative stereochemistry was determined by NOESY spectroscopy. IR (neat): 2967, 2371, 1597 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.51 (d, *J* = 7.0 Hz, 3 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 1.96 (sept d, *J* = 7.0, 2.5 Hz, 1 H), 2.37 (s, 3 H), 2.54 (dd, *J* = 17.0, 9.0 Hz, 1 H), 2.68 (dd, *J* = 17.0, 7.0 Hz, 1 H), 2.97–3.02 (m, 1 H), 4.33 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.10–7.15 (m, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.30 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 17.4, 21.0, 21.6, 29.0, 40.7, 69.3, 118.2, 119.5, 121.8, 126.1, 126.9, 128.9, 129.7, 134.9, 135.2, 142.8, 144.2. HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_2NaO_2S$: 377.1294; found: 377.1294.

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