Alkenyl Isocyanide Conjugate Additions: A Rapid Route to γ-Carbolines

Dr. Sergiy V. Chepyshev[a], **Prof. Dr. J. Armando Lujan-Montelongo**[b], **Allen Chao**[a], and **Prof. Fraser F. Fleming**[a]

[a]Department of Chemistry, Drexel University, 32 South 32nd St., Philadelphia, PA 19104

[b]Departmento de Química, Centro de Investigación y de Estudios Avanzados (Cinvestav), Av. Instituto Politécnico Nacional 2508, Ciudad de México, México 07360

Abstract

Isocyanides are exceptional building blocks whose wide deployment in multi-component and metal insertion reactions belies their limited availability. Addressing this deficiency is the first conjugate addition-alkylation method. An array of organolithiums, magnesiates, enolates, and metalated nitriles, add conjugately to β- and β, β-disubstituted arylsulfonyl alkenyl isocyanides to rapidly assemble diverse isocyanide scaffolds. The intermediate metalated isocyanides are efficiently trapped with electrophiles to generate substituted isocyanides incorporating contiguous tri- and tetra-substituted centers. The substituted isocyanides are ideally functionalized for elaboration into synthetic targets as illustrated by the three-step synthesis of the γ-carboline, *N*-methyl ingenine B.

Graphical Abstract

Conjugate addition of diverse organometallics to sulfonyl-substituted alkenyl isocyanides overcomes the historical challenge of rapidly assembling complex isocyanides that retain the isocyanide functionality. The strategy affords complex isocyanides that are poised for elaboration into heterocycles as illustrated with the three-step synthesis of *N*-methyl ingenine B.
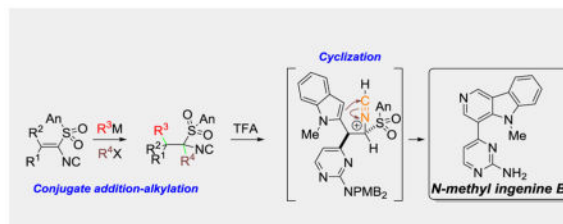
Keywords

isocyanide; conjugate addition; organometallics; γ-carboline; *N*-methyl ingenine B

Correspondence to: Fraser F. Fleming.

Isocyanides are unusual carbon-based functional groups in formally containing a carbon atom with a free electron pair.[1] The carbene-like structure (Figure 1)[2] confers ambiphilic reactivity on the isocyanide carbon that manifests an exceptionally diverse reactivity for one functional group: metal insertion,[3] radical additions,[4] nucleophilic additions,[1] and electrophilic alkylations.[5] The high reactivity toward disparate reagents is particularly valuable for multicomponent reactions,[5] heterocycle synthesis,[6] and accessing acyclic nitrogenous scaffolds.[6]

Isocyanide-containing metabolites, mostly from marine sources,[7] epitomize the challenge in working with isocyanides; the reactive carbene-like carbon confers biological activity through the same type of bonding that creates a susceptability of the R-NC unit toward irreversable complexation to transition metals, hydrolysis, and oxidation.[1] The tenacity of isocyanides to ligate to transition metals results from a strong σ-donation of the electron pair on carbon coupled with a symbiotic removal of electron density from the metal into the RN≡C π*-orbitals.[8]

The high reactivity and delicate nature of isocyanides, combined with the propensity to coordinate transition metals, has caused a severe deficiency of methods for manipulating the carbon scaffold while retaining the isocyanide functionality.[1] Most isocyanides are installed through a late-stage, three-step sequence: amine deprotection, formylation, and dehydration.[9] Described below is the first conjugate addition-alkylation of alkenyl isocyanides employing main group organometallics which effectively expands the limited repertoire of isocyanide-based bond constructions.

The viability of using main group organometallics to develop a general conjugate addition to unsaturated isocyanides was predicated on sporadic additions of Grignards[10] and sulfur ylides[11] to isocyanoacrylates. Initial forays to develop the conjugate addition employed the alkenyl isocyanide **3a**, derived from TosMIC (**2a**, Scheme 1).[12] Exploratory additions of BuMgCl, Me$_2$CuLi, and Et$_2$BuZnLi[13] to **3a** afforded a complex mixture of products, suggesting that the process involves more than a simple addition to a vinyl sulfone.[14] Further screening led to promising additions with BuLi (24%) and the magnesiate Bu$_3$MgLi[15] (62%, Scheme 1).

Attempts to expand the conjugate additions to **3a** with additional organometallics led to an effective reaction with lithiated dithiane (Table 1, entry 1) but identified two limitations: poor tolerance of structural diversity in the organometallic and a pronounced instability of the resulting isocyanides toward storage and purification.[16] The limitations stimulated tuning the electronic and steric nature of the arylsulfone substituent to maximize reactivity and stability (Table 1).[17] Electron deficient arylsulfonyl-substituents were anticipated to facilitate the conjugate addition but the adduct from addition of Bu$_3$MgLi to the trifluoromethyl-substituted isocyanide **3b** was particularly unstable (Table 1, entry 2). Incorporating o-CF$_3$ and o-OMe substituents (**3c**) improved the conjugate addition with PhLi and lithiated dithiane but the resulting isocyanides **6a** and **6b** were prone to decompose during purification (Table 1, entries 3 and 4).[16] Speculating that the efficacy of **3c** was due to precomplexation between the organometallic and the o-OMe,[18] led to evaluation of di-o-methoxyphenylisocyanide **3d** and o-anisyl (An) isocyanide **3e**. While the addition of

Bu$_3$MgLi to **3d** afforded a modest yield of **7a**, the *o*-anisyl isocyanide **3e** efficiently reacted with Bu$_3$MgLi and BuLi to afford stable 8a in 54% and 53% yield, respectively (Table 1, entry 6).

The generality of the conjugate additon to (*o*-anisyl)sulfonyl alkenyl isocyanides was probed with a variety of organometallics (Table 2). Diverse organolithiums with sp^3, sp^2- and sp-hybridization readily added to (*o*-anisyl)sulfonyl alkenyl isocyanides **3** (Table 2, **8b–8d**, **8e–8i**, and **8j**, respectively).[19] The conjugate addition of MeLi to afford **8b**, initially performed at temperatures between −100 to −95 °C (62% yield), was found to be more readily performed, and in higher yield, with MeLi·LiBr at −78 °C (72% yield). Selective allyl and benzyl additions[20] were performed from the mixed organomagnesiates allylMgBu$_2$Li and BnMgBu$_2$Li to afford isocyanides **8k** and **8l**, respectively. Lithiated acetonitrile and lithiated cyclohexanecarbonitrile afforded the nitrile-containing isocyanides **8m–8o**, two of which contain quaternary centers. The lithium enolate derived from ethyl 2-methylpropionate afforded ester-isocyanide **8p**, also installing a quaternary center. Conjugate reduction with NaBH$_4$ afforded the alkylisocyanides **8q** to **8s**, which provides a valuable route to branched isocyanides.[21]

The conjugate additions generated metalated isocyanides that were effectively intercepted by electrophiles (Table 3). Initial optimization focused on the methylation of the lithiated isocyanide derived from addition of PhLi to **3e**. Methylation afforded **9a** (53%) with incomplete conversion; addition of HMPA or DMPU (4 equiv) improved the reaction efficiency to 74% and 79%, respectively (Table 3, entry 1). DMPU-promoted electrophilic capture led to efficient addition-alkylations of **3e** with PhLi and PrI (Table 3, entry 2) and addition-methylations with lithiated *N*-methyl indole and lithiated benzofuran (Table 3, entries 3–4). The conjugate addition-alkylation provides a valuable method to sterically encumbered alkylisocyanides that are challenging to prepare by direct alkylation of sulfinylmethylisocyanides such as TosMIC (**2a**).[24]

Mechanistically the conjugate addition likely proceeds through a preassociation of the organometallic with the sulfone and anisyl oxygens (Scheme 2).[18] Close proximity between the nucleophilic organometallic and the alkenyl isocyanide would facilitate intramolecular delivery of the alkyl group to the β-carbon (**10**) while preventing attack on the isocyanide. Complexation within the resultant lithiated isocyanide **11** may retard the alkylation which DMPU assists by solvation to a more nucleophilic, and accessible, solvent-separated ion pair (**12** → **13**).

The conjugate addition affords substituted isocyanides that are ideally functionalized for heterocyclic synthesis. Rapid access to the indole-containing isocyanides **8h** and **9d** prompted cyclization to the γ-carboline scaffold,[25] an emerging pharmacophore.[26] Optimization experiments revealed that substoichiometric TFA triggered an efficient cyclization with (1*S**, 2*R**)-**8h** or **9d** (Scheme 3).[27] Generation of the nitrilium ion **14** likely triggers cyclization to imine **15** which eliminates sulfinic acid to afford γ-carboline **16**.[28] Rapid access to the γ-carboline **16a**[29] is significant because of their potential as hepatitis C inhibitors.[30]

The versatility of the isocyanide conjugate addition-cyclization is illustrated in the synthesis of *N*-methyl ingenine B (**20**, Scheme 4).[31] In situ silylation-olefination of **2b**[12] with aldehyde **17**[32] afforded alkenyl isocyanide **18** that participated in a smooth conjugate addition with lithiated *N*-methylindole to provide **19** (Scheme 4). (1*S**, 2*R**)-**19**[33] was efficiently converted to *N*-methyl ingenine B (**20**)[34] on exposure to TFA, a process involving cyclization, sulfinate elimination, and debenzylation.

Main group organometallics react with (*o*-anisyl)sulfonyl al-keneisocyanides in the first conjugate addition-alkylation of alkenyl isocyanides. Diverse organolithiums, magnesiates, enolates, and metalated nitriles, afford metalated isocyanides that are readily intercepted by electrophiles to efficiently install contiguous tri- and tetra-substituted centers. The highly-substituted isocyanides are ideally functionalized for elaboration into synthetic targets as illustrated by the three-step synthesis of the γ-carboline, *N*-methyl ingenine B (**20**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Suginome, M., Ito, Y. Science of Synthesis. Murahashi, S-I., editor. Vol. 19. Thieme; Stuttgart: 2004. p. 445-530.

2. Ramozzi R, Chéron N, Braïda B, Hiberty PC, Fleurat-Lessard P. New J Chem. 2012; 36:1137.

3. Chakrabarty S, Choudhary S, Doshi A, Liu FQ, Mohan R, Ravindra MP, Shah D, Yang X, Fleming FF. Adv Synth Cat. 2014; 356:2135.

4. Zhang B, Studer A. Chem Soc Rev. 2015; 44:3505. [PubMed: 25882084]

5. a) Zhu, J., Wang, Q., Wang, M-X. Multicomponent Reactions in Organic Synthesis. VCH; Weinheim: 2014. b) Dömling A. Chem Rev. 2006; 106:17. [PubMed: 16402771] c) Zhu J. Eur J Org Chem. 2003:1133.

6. Nenajdenko, VG. Isocyanide Chemistry: Applications in Synthesis and Material Science. VCH; Weinheim: 2012.

7. a) Mancini I, Guella G, Defant A. Mini Rev Med Chem. 2008; 8:1265. [PubMed: 18855740] b) Garson MJ, Simpson JS. Nat Prod Rep. 2004; 21:164. [PubMed: 15039841] c) Chang CWJ. Prog Chem Org Nat Prod. 2000; 80:1.d) Edenborough MS, Herbert RB. Nat Prod Rep. 1988; 5:229. [PubMed: 3067133]

8. Lazar, M., Angelici, RJ. Modern Surface Organometallic Chemistry. Basset, J-M.Psaro, R.Roberto, D., Ugo, R., editors. Vol. Ch. 13. VCH; Weinheim: 2009. p. 513-556.

9. Huters AD, Styduhar ED, Garg NK. Angew Chem Int Ed. 2012; 51:3758.Angew Chem. 2012; 124:3820.

10. Schöllkopf U, Meyer R. Angew Chem Int Ed. 1975; 14:629.Angew Chem. 1975; 87:624.

11. a) Honma M, Kirihata M, Uchimura Y, Ichimoto I. Biosci Biotech Biochem. 1993; 57:659.b) Kirihata M, Sakamoto A, Ichimoto I, Ueda H, Honma M. Agric Biol Chem. 1990; 54:1845.c) Schöllkopf U, Harms R, Hoppe D. Liebigs Ann Chem. 1973:611.

12. Van Leusen AM, Wildeman J. Rec Trav Chim Pays-Bas. 1982; 101:202.

13. a) Hevia E, Chua JZ, García-Álvarez P, Kennedy AR, McCall MD. Proc Natl Acad Sci USA. 2010; 107:5294. [PubMed: 20212145] b) Merkel S, Stern D, Henn J, Stalke D. Angew Chem Int Ed. 2009; 48:6350.Angew Chem. 2009; 121:6468.

14. El-Awa A, Noshi MN, du Jourdin XM, Fuchs PL. Chem Rev. 2009; 109:2315. [PubMed: 19438205]

15. a) Mongin F, Harrison-Marchand A. Chem Rev. 2013; 113:7563. [PubMed: 23952912] b) Krasovskiy A, Straub BF, Knochel P. Angew Chem Int Ed. 2006; 45:159.Angew Chem. 2005; 118:165.

16. Some isocyanides hydrolyze during silica gel chromatography while others exhibit a pronounced tendency toward irreversible adsorption: Kotha S, Sreenivasachary N. Bioorg Med Chem Lett. 1998; 8:257. [PubMed: 9871665] Kotha S, Brahmachary E, Sreenivasachary N. Tetrahedron Lett. 1998; 39:4095.

17. Lujan-Montelongo JA, Estevez AO, Fleming FF. Eur J Org Chem. 2015:1602.

18. Whisler MC, MacNeil S, Snieckus V, Beak P. Angew Chem Int Ed. 2004; 43:2206.Angew Chem. 2004; 116:2256.

19. Two exceptions are vinyllithium (17% yield of the conjugate adduct) and *t*BuLi; the main product is an unstable imine resulting from addition to the isocyanide.

20. So nicki JG. Tetrahedron Lett. 2006; 47:6809.

21. van Leusen D, van Leusen AM. Synthesis. 1991:531.

22. The diastereomeric ratios were determined by ^{1}H NMR integration of diagnostic methine signals in the crude reaction mixture.

23. (1*S**, 2*S**)-**8d** was a crystalline solid whose structure was determined by x-ray crystallography. Determination of the relative stereochemistry for (1*S**, 2*S**)-**8d** allowed assignment of the diagnostic methine signals that provided a signature for the assignments of the isocyanides **8** in Table 1. Krishna PR, Prapurna YL. Synlett. 2009:2613.

24. van Leusen AM, Bouma RJ, Possel O. Tetrahedron Lett. 1975; 16:3487.

25. a) Pilipenko AS, Uchuskin MG, Trushkov IV, Butin AV. Tetrahedron. 2015; 71:8786.b) Nissen F, Richard V, Alayrac C, Witulski B. Chem Commun. 2011; 47:6656.c) Ding S, Shi Z, Jiao N. Org Lett. 2010; 12:1540. [PubMed: 20210308] d) Alekseyev RS, Kurkin AV, Yurovskaya MA. Chem Heterocycl Comp. 2009; 45:889.

26. a) Salim MTA, Goto Y, Hamasaki T, Okamoto M, Aoyama H, Hashimoto Y, Musiu S, Paeshuyse J, Neyts J, Froeyen M, Herdewijn P, Baba M. Antiviral Res. 2010; 88:263. [PubMed: 20869990] b) Chen J, Dong X, Liu T, Lou J, Jiang C, Huang W, He Q, Yang B, Hu Y. Bioorg Med Chem. 2009; 17:3324. [PubMed: 19359185]

27. Although treating the (1*S**, 2*S**)-diastereomer with TFA afforded a complex mixture, the (1*S**, 2*S**)-diastereomers were readily equilibrated with *t*-BuOK.

28. Livinghouse T. Tetrahedron. 1999; 55:9947.

29. Zhang, H. PhD thesis. Iowa State University (IA); 2003.

30. Aoyama H, Sako K, Sato S, Nakamura M, Miyachi H, Goto Y, Okamoto M, Baba M, Hashimoto Y. Heterocycles. 2009; 77:779.

31. Ingenine B, *des*-methyl **20**, exhibits pronounced cytotoxicity against murine lymphoma: Ibrahim SRM, Mohamed GA, Zayed MF, Sayed HM. Drug Res. 2015; 65:361.

32. See the supporting information for synthetic details.

33. Equilibration of (1*S**, 2*S**)-**19** with *t*-BuOK afforded a 1:1 ratio of (1*S**, 2*S**)- and (1*S**,2*R**)-**19** whose purification afforded pure (1*S**, 2*R**)-**19** (37%), pure (1*S**, 2*S**)-**19** (35%), and a 1:1 mixture of (1*S**,2*R**)- and (1*S**,2*S**)-**19** (15%).

34. An oxidative demethylation was successfully performed on **16a** but application of the same sequence to *N*-methyl ingenine B (**20**) caused significant degradation.
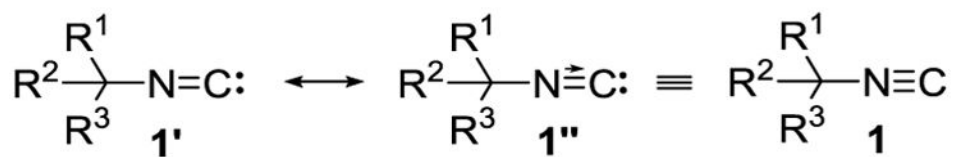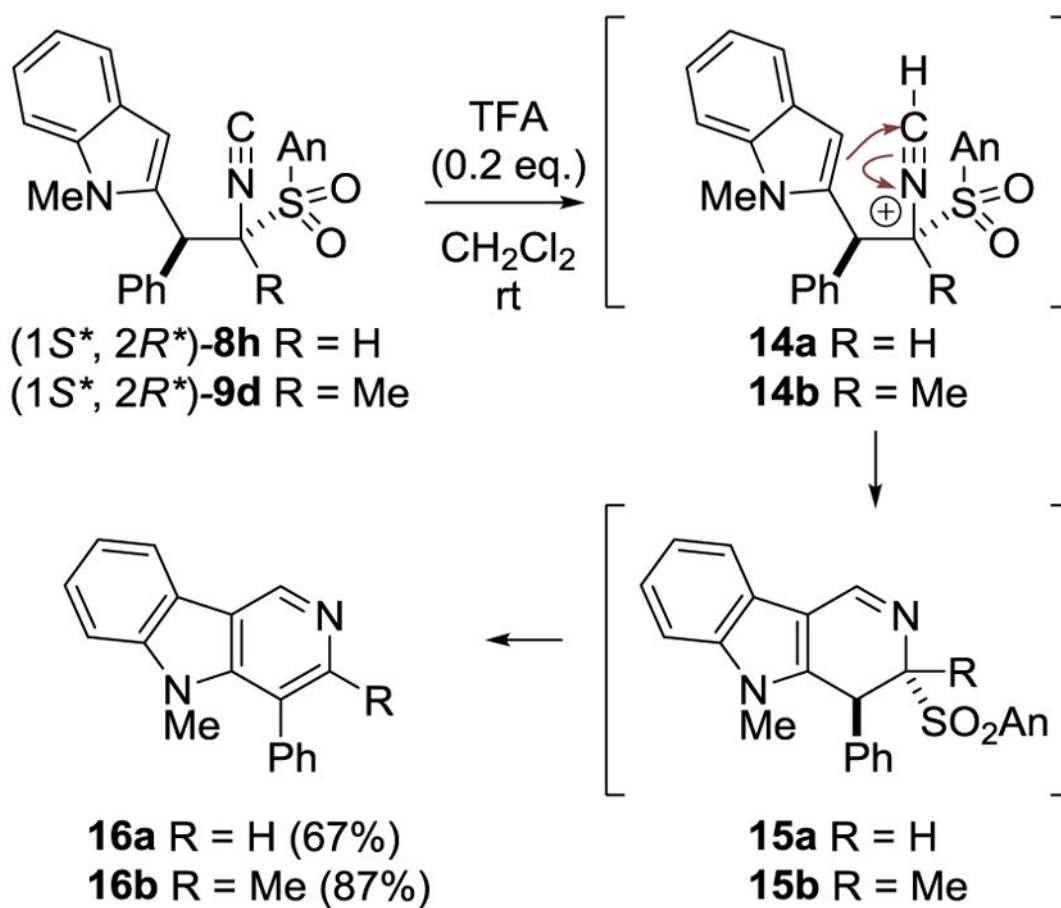
Figure 1.
Isocyanide representations.
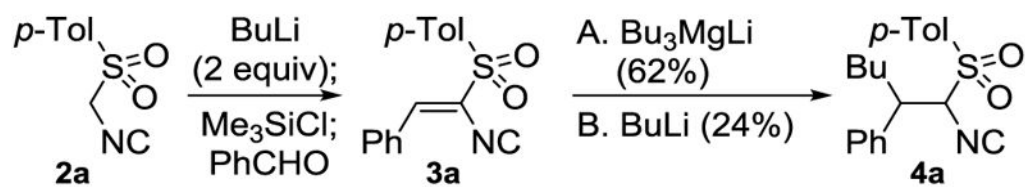
Scheme 1.
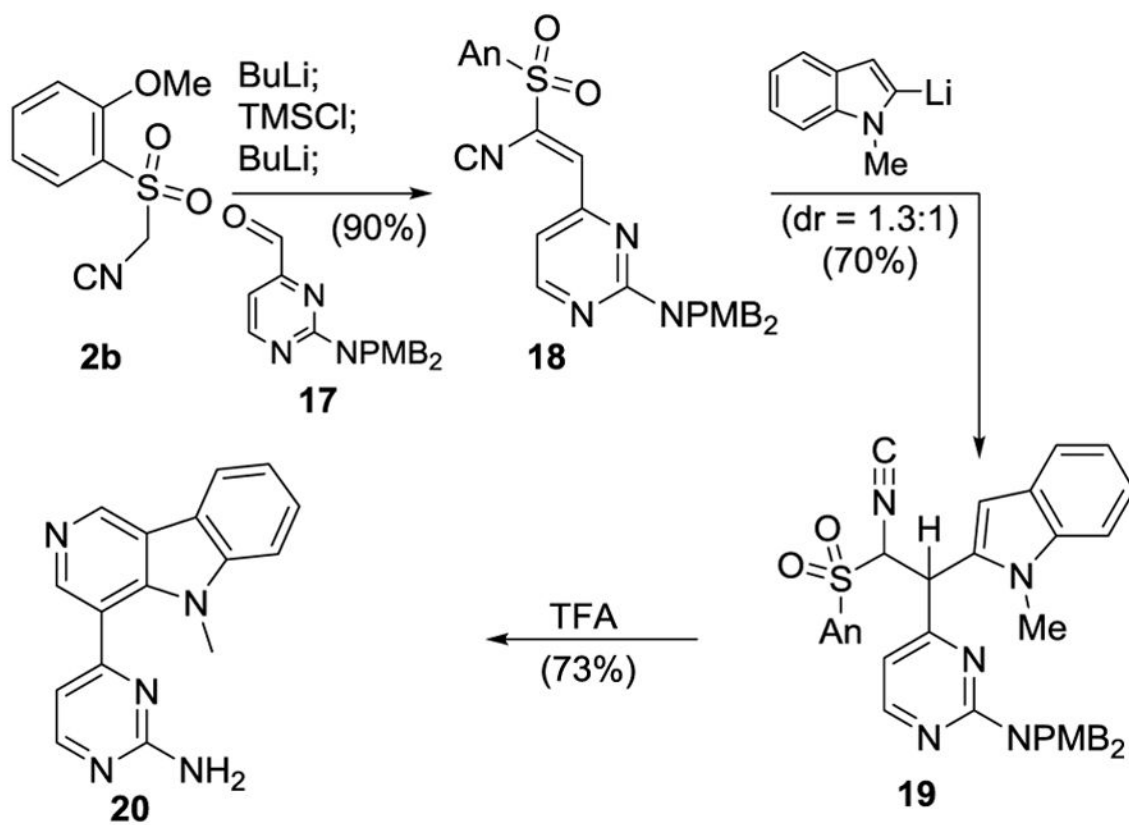Synthesis and addition to sulfonylisocyanide **3a**.
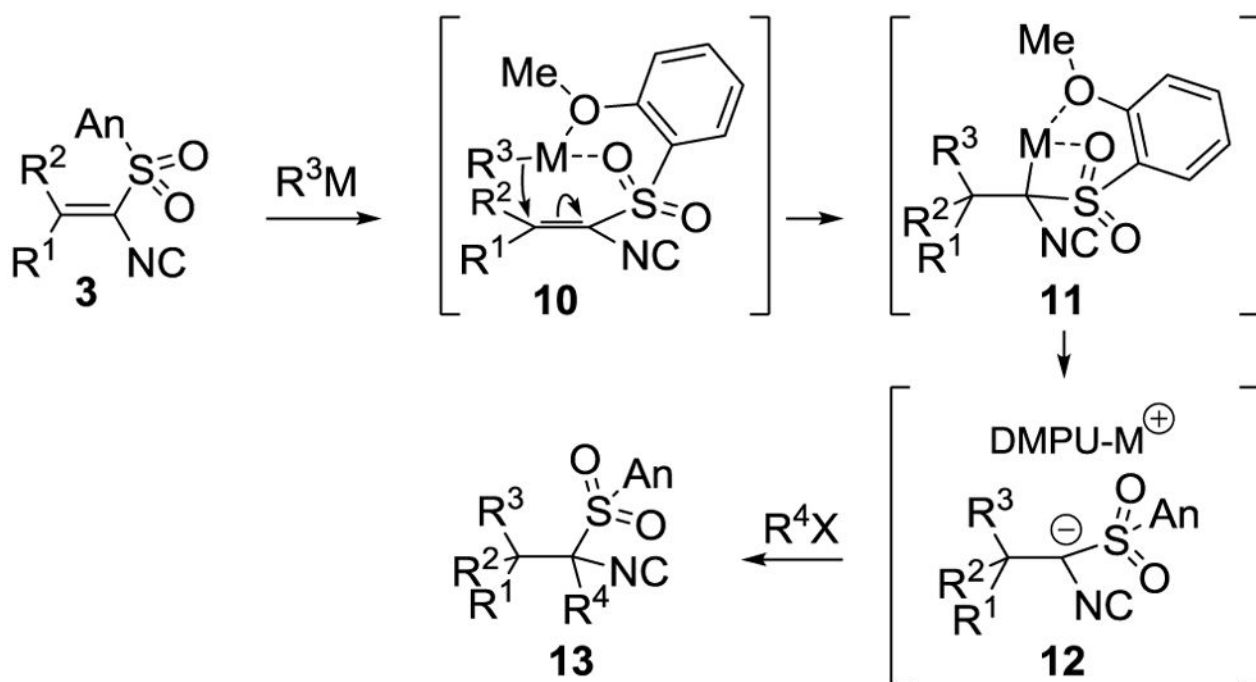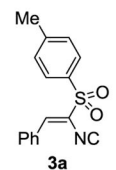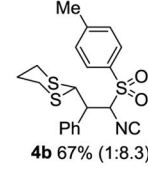
Scheme 2.
Conjugate addition-alkylation mechanism.

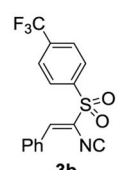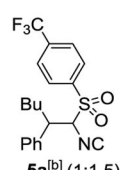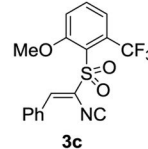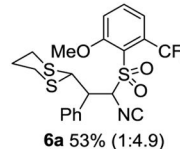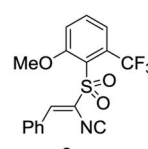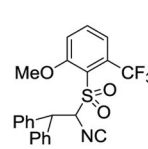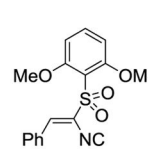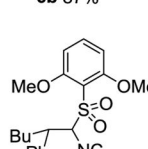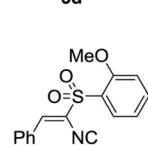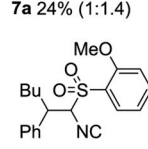**Scheme 3.**
Isocyanide cyclization to γ-carbolines.

Scheme 4.
Synthesis of N-Methyl ingenine B (**20**).

Table 1

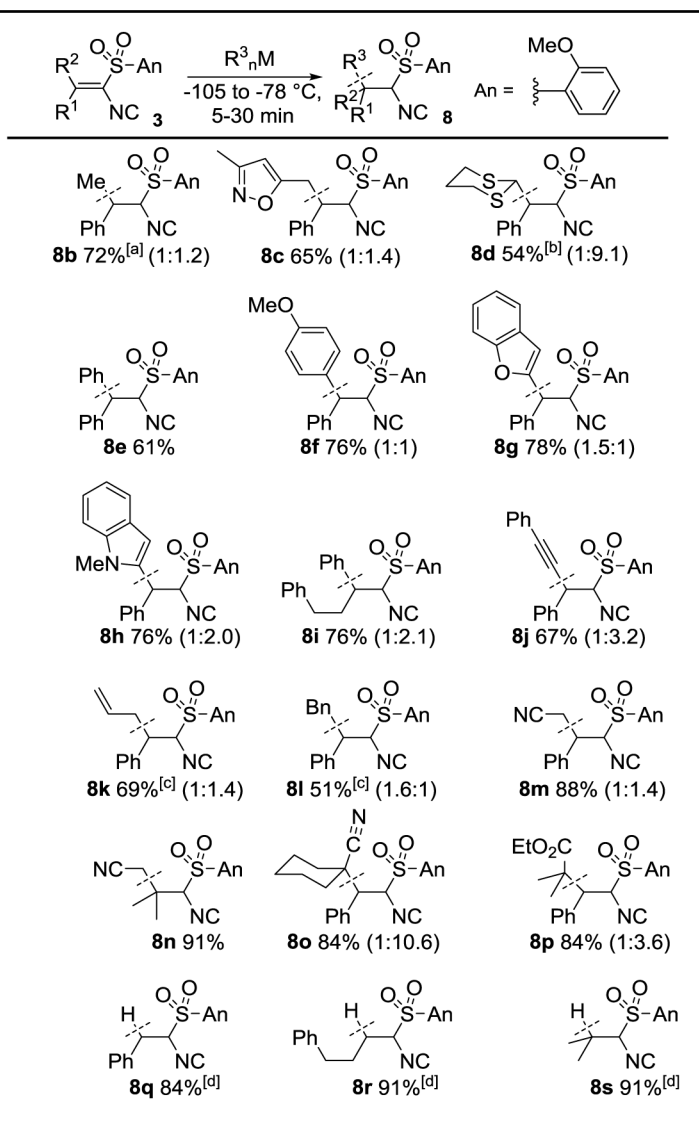Dependence of conjugate addition efficiency on sulfone structure.

Entry	Sulfonyl isocyanide	Nucleophile	Yield [%] (dr)[a]
1	3a		4b 67% (1:8.3)
2	3b	Bu₃MgLi	5a[b] (1:1.5)
3	3c		6a 53% (1:4.9)
4	3c	PhLi	6b 87%
5	3d	Bu₃MgLi	7a 24% (1:1.4)
6	3e	A. Bu₃MgLi B. BuLi	8a (A 54%, B 53%) (1:1.8)

[a] The diastereomeric ratios were determined by ^{1}H NMR integration of diagnostic methine signals.

[b] The isocyanide was unable to be purified for characterization.
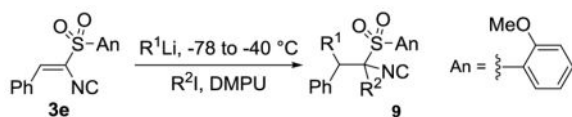
Table 2

Conjugate additions to *o*-anisylsulfonyl alkenisocyanides **3**.

Table 3

Conjugate addition-alkylations with alkenyl isocyanide **3e**.

Entry	R^{1}Li	R^{2}I	Alkaneisocyanide yield [%] (dr)[a]
1	PhLi	MeI	**9a** 79%
2	PhLi	PrI	**9b** 82%
3	(benzofuran-2-yl)Li	MeI	**9c** 82% (3:2:1)
4	(1-methylindol-2-yl)Li	MeI	**9d** 63%[b] (4:0:1)

[a] The diastereomeric ratios were determined by ^{1}H NMR integration of diagnostic methine signals in the crude reaction mixture.

[b] The configuration was unambiguously secured by x-ray diffraction.