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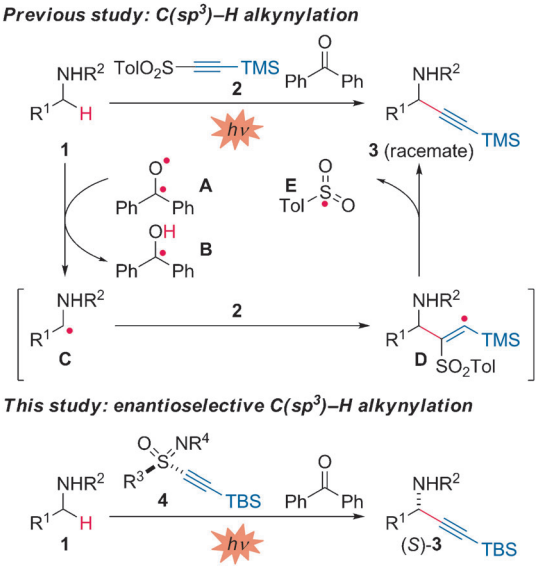
Enantioselective Radical Alkynylation of C(sp^3)-H Bonds Using Sulfoximine as a Traceless Chiral Auxiliary

Masanori Nagatomo, Shun Yoshioka, and Masayuki Inoue*[a]

Abstract: Enantioselective alkynylation of C(sp^3)–H bonds adjacent to a nitrogen atom has been achieved using only chiral *p*-tolyl *tert*-butyldimethylsilylethynyl sulfoximine and benzophenone under photo-irradiation conditions. A two-carbon alkyne unit was chemo- and enantioselectively transferred at the nitrogen-substituted methylene to produce the optically active propargylic amines of various structures. Remarkably, the NH-unprotected sulfoximine group efficiently transmits its stereochemical information to the product and functions as a traceless chiral auxiliary.

Enantio-enriched propargylic amines serve as precursors for a variety of chiral materials since the nitrogen atom and alkyne are versatile handles for further transformation.[1] Among the numerous methods to access optically active propargylic amines, enantioselective direct alkynylation of C(sp^3)–H bonds adjacent to nitrogen has attracted significant attention[2] because it eliminates pre-activation steps and thus greatly simplifies the overall synthetic scheme. However, the realization of such useful reactions is a significant challenge mainly due to the lack of general strategies for selective functionalization of a specific C(sp^3)–H bond over the numerous C–H bonds in organic molecules. Important progress on asymmetric intermolecular C(sp^3)–C(sp) bond formation was recently reported based on transition-metal-catalyzed C(sp^3)–H bond activation.[3,4] On the other hand, there is no example of the metal-free enantioselective conversion of C(sp^3)–H bonds to C(sp^3)–C(sp) bonds to date.[5]

We recently reported a chemoselective photochemical alkynylation of alkyl amine derivative **1** using $Ph_2C{=}O$ and 1-tosyl-2-(trimethylsilyl)acetylene **2** (Scheme 1).[6–8] In this transformation, the electrophilic oxyl radical **A**, which is photo-activated from benzophenone, chemoselectively abstracts the hydrogen from the electron-rich nitrogen-substituted methylene of **1** to furnish carbon radical **C**. Reaction between **C** and the electron-deficient alkyne **2** occurs at the



Scheme 1. Previously reported direct alkynylation of C(sp^3)–H bonds and the present enantioselective alkynylation strategy.

α-position of the sulfonyl group by avoiding unfavorable steric interaction with the bulky TMS group. Subsequent release of the tosyl radical **E** from the produced vinyl radical intermediate **D** results in formation of the alkynylated product **3** as a racemate.[9]

We envisioned that the use of the chiral ethynyl sulfoximine derivative **4** instead of achiral **2** would enable enantioselective formation of either (*S*)-**3** or (*R*)-**3**. Here we report the direct asymmetric alkynylation of C(sp^3)–H bonds adjacent to a nitrogen atom using **4** under photo-irradiation conditions.[10] In the present reaction, the sulfoximine group of **4** not only transmits its chirality to the product but also acts as a traceless chiral auxiliary. This unique radical-based method provides a new synthetic strategy for rapid construction of various optically active propargylic amines.

The various ethynyl sulfoximines were synthesized from enantiopure sulfinates as represented by preparation of **4b** and **4i** in Scheme 2.[11] Nucleophilic attack of the Grignard reagent on the sulfur atom of (–)-menthyl (*S*)-*p*-toluenesulfinate **5** produced *p*-tolyl *tert*-butyldimethylsilylethynyl sulfoxide **6**.[12,13] Imination of **6** using catalytic [$Rh_2(OAc)_4$] and stoichiometric trifluoroacetamide and iodobenzene diacetate occurred with retention of configuration, leading to the corresponding *N*-trifluoroacetyl protected sulfoximine **4b**.[14]

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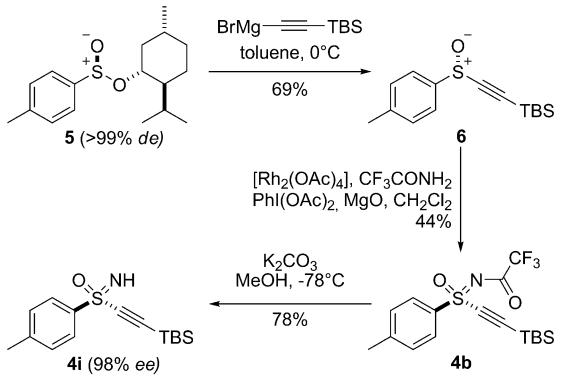


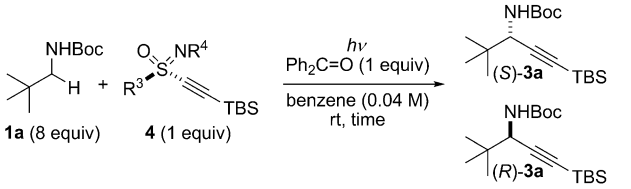
Scheme 2. Preparation of enantiopure *p*-tolyl *tert*-butyldimethylsilylethynyl sulfoximine.

Chemoselective cleavage of the *N*-acyl bond of **4b** in the presence of the TBS group was realized by performing methanolysis at low temperature to produce the *N*-unprotected **4i**.

To investigate the structural requirements of the *S*- and *N*-substituents (R^3 and R^4, respectively) for high enantioselectivity, nine sulfoximine derivatives, **4a–i**, were subjected to reaction with *tert*-butyl neopentylcarbamate **1a** (Table 1). When a mixture of *N*-*p*-toluenesulfonyl *p*-tolylsulfoximine **4a**, $Ph_2C{=}O$ (1 equiv), and **1a** (8 equiv) in benzene was photo-irradiated, product **3a** was indeed obtained, albeit with low enantioselectivity (entry 1). Changing the solvent from benzene to *t*BuOH (entry 2) or replacing the *N*-tosyl group with the *N*-trifluoroacetyl group (**4b**, entry 3) had only a small effect on the enantioselectivity. Therefore, a series of methylsulfoximine derivatives, **4c–h**, were applied to the alkynylation (R^3 = Me, entries 4–9). The selectivity toward (*R*)-**3a** was improved upon use of *N*-*p*-tosyl methylsulfoximine **4c** (entry 4). Replacement of *p*-tosyl with *o*-tosyl (entry 5), mesyl (entry 7), or trifluoroacetyl (entry 8) groups did not increase the (*R*)-selectivity, while the *o*-nosyl group inhibited the photo-reaction (entry 6). Surprisingly, the reaction with *N*-non-substituted **4h** exhibited the opposite (*S*)-selectivity, providing (*S*)-**3a** in 73:27 er (entry 9). Finally, *N*-nonsubstituted *p*-tolylsulfoximine **4i** was found to be the optimal structure for inducing high enantioselectivity (entry 10). Using three equivalents of $Ph_2C{=}O$ (entry 11) furnished (*S*)-**3a** in 65% yield and 84:16 er from **4i** (entry 11). It is particularly noteworthy that minimal structural change at the sulfur atom from achiral **2** to chiral **4i** (O→NH) provided the maximum increase in enantioselectivity.

The generality of chiral agent **4i** was demonstrated by its application to a variety of secondary C–H bonds adjacent to nitrogen-based functional groups (Table 2). As compared with the branched neopentylcarbamate **1a**, the linear pentylcarbamate **1b** was converted into the product **3b** in lower

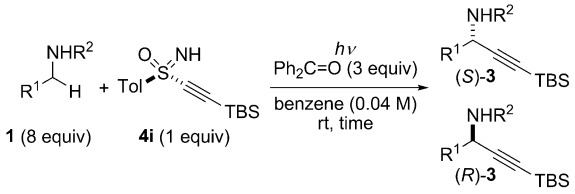
Table 1. Screening of chiral alkynyl sulfoximines.[a]

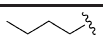
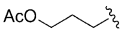
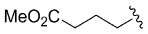
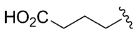


Entry	4	R^3	R^4	*t* [h]	Product **3a** Yield[b] [%]	er (*S*:*R*)[c]
1	**4a**	Tol	*p*-Ts	7	62[d]	44:56
2[e]	**4a**	Tol	*p*-Ts	24	56	40:60
3	**4b**	Tol	$COCF_3$	4.5	56	36:64
4	**4c**	Me	*p*-Ts	7	57	28:72
5	**4d**	Me	*o*-Ts	13	46	30:70
6	**4e**	Me	*o*-Ns	24	0	–
7	**4f**	Me	Ms	12	48	30:70
8	**4g**	Me	$COCF_3$	5	33	27:73
9	**4h**	Me	H	9	18	73:27
10	**4i**	Tol	H	24	44	81:19
11[f]	**4i**	**Tol**	**H**	**24**	**65**[d]	**84:16**

[a] Conditions: *tert*-butyl neopentylcarbamate **1a** (8 equiv), chiral alkynyl sulfoximine **4** (1 equiv), $Ph_2C{=}O$ (1 equiv), benzene (0.04 M), at rt for the indicated time (5–24 h) under Ar atmosphere, photo-irradiation using a Riko 100W medium pressure lamp. [b] Yield was calculated based on NMR analysis of the crude mixture unless otherwise noted. [c] Determined by ^1H NMR analysis of the corresponding (−)-MTPA amide. [d] Isolated yield. [e] Reaction was conducted in *t*BuOH (0.04 M). [f] 3 equiv of $Ph_2C{=}O$ was used.

Table 2. Enantioselective alkynylation of *N*-substituted C(sp^3)–H bonds of various structures.[a]



Entry	1	R^1	R^2	Product **3** Yield[b] (%)	er (*S*:*R*)[c]
1	**1b**		Boc	66	66:34
2	**1c**		Cbz	68	75:25
3	**1d**		Bz	59	76:24
4	**1e**		Ac	75	83:17
5	**1f**		Ac	57	89:11
6	**1g**		Ac	86	80:20
7	**1h**		Ac	77	82:18
8	**1i**		Ac	51	84:16
9	**1j**		Ac	79	83:17
10	**1k**		Ac	53	81:19
11	**1l**		Ac	49	78:22
12	**1m**		Ac	33	72:28

[a] Conditions: *N*-protected-alkylamine **1b–1m** (8 equiv), chiral alkynyl sulfoximine **4i** (1 equiv), and $Ph_2C{=}O$ (3 equiv) in benzene (0.04 M) at room temperature for 5–24 h under photo-irradiation using a Riko 100 W medium pressure lamp. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the corresponding (−)-MTPA amide (entries 1, 8, 10–12) or by HPLC using a chiral stationary phase (entries 2–7, 9).

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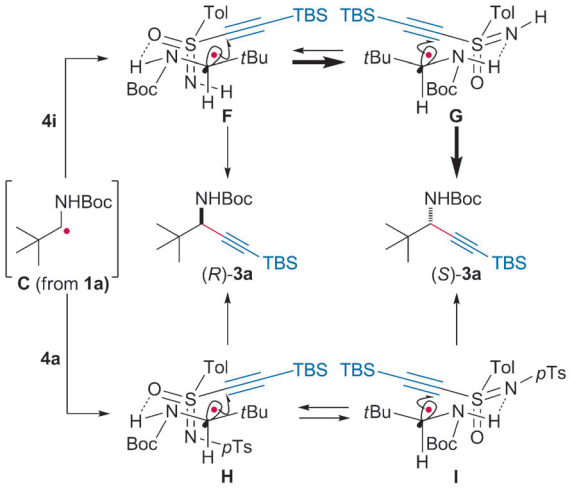
enantiomer ratio under the same reaction conditions (entry 1).[15] Thus, the *N*-protective group was changed from Boc in entries 2–4. Among the four different groups (Boc, Cbz, Bz, and Ac), the Ac group (**1e**) was found to be best in terms of selectivity (83:17 er, entry 4). The favorable effect of the Ac group was confirmed by comparison of the enantiomer ratios of the Ac-protected neopentylamine **3f** and the Boc-protected **3a** (89:11 in entry 5, Table 2 vs. 84:16 in entry 11, Table 1). Moreover, three structurally different aliphatic acetyl amides, **1g–i**, reacted efficiently with **4i** to provide the corresponding propargyl amides, **3g–i**, in high enantioselectivity (entries 6–8). The protected amino alcohol **1j** underwent alkynylation chemoselectively at the *N*-substituted methylene over the *O*-substituted counterpart,[6] giving rise to the adduct **3j** (entry 9). The ester (**1k**), the free carboxylic acid (**1l**), and the bromide (**1m**) were all tolerant to the photo-induced radical alkynylation, furnishing the enantio-enriched products, **3k–m** (entries 10–12). The newly introduced stereocenters of the products were established to be (*S*)-configured.

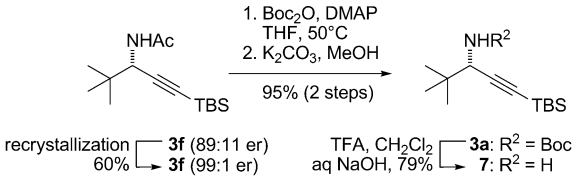
The results in Tables 1 and 2 demonstrated that the chirality of the sulfoximine group of *N*-non-substituted *p*-tolyl sulfoximine **4i** was efficiently transferred to the nitrogen atom substituted carbon center. Rationalization of the enantioselective formation of (*S*)-**3a** from **1a** is shown in Scheme 3.



Scheme 3. Plausible explanation for enantioselective formation of (*S*)-**3a** from **1a**.

Since the difference in the steric size of O and NH at the sulfur atom of **4i** is negligible, we reasoned that the enantioselective outcome would originate from their distinct hydrogen bond capabilities. Carbon radical **C** generated from **1a** potentially forms two six-membered chair-like transition states, **F** and **G**, in which all the bulky groups (Tol, Boc, *t*Bu) adopt equatorial orientations. The higher basicity of HN=S compared to O=S causes HN=S to hydrogen bond with HNBoc more strongly, resulting in formation of (*S*)-**3a** via the more populated **G**.[16,17] This explanation is supported by the observed low enantioselectivity upon use of *N*-*p*-tosyl substituted sulfoximine **4a** (Table 1, entry 1). The additional *p*-tosyl group decreased the basicity of the N of **4a**, and thus the strength of hydrogen bonding in **I** is similar to that in **H**. Accordingly, (*R*)-**3a** and (*S*)-**3a** are generated non-selectively from **H** and **I**, respectively. Although the mechanism remains to be clarified in more detail, use of the *N*-free sulfoximine as the hydrogen bond acceptor should have wider applications in designing asymmetric reactions beyond the present work.

As exemplified in Scheme 4, the enantiopure propargyl amines were easily prepared from the thus obtained Ac-protected products. Because of its highly crystalline nature, one recrystallization of **3f** (89:11 er) afforded enantiopure **3f**



Scheme 4. Recrystallization and deprotection of **3f**.

(99:1 er). The Ac group of **3f** was converted into the Boc group of **3a** by treating with Boc_2O and DMAP, and subsequently with K_2CO_3 and MeOH.[18] Acid-promoted deprotection of **3a** gave rise to the free amine **7**.

In summary, *p*-tolyl *tert*-butyldimethylsilylethynyl sulfoximine **4i** and benzophenone effected chemo- and enantioselective C(sp^3)-H alkynylation at the nitrogen-substituted methylene under photo-irradiation conditions. Since cleavage of the sulfoximine moiety from **4i** takes place during the reaction, no additional step is required for removal of the chiral auxiliary from the product. This operationally simple metal-free transformation proceeds in a predictable fashion in terms of enantioselectivity, generating various optically active propargylic amines. The *N*-protective group and TBS-acetylide moiety of the products can serve as versatile handles for further functionalizations; consequently, the present radical-based methodology will be useful for efficient preparation of substructures of nitrogen-containing natural products and pharmaceuticals.

Experimental Section

The experimental procedures and the characterization of the compounds studied herein can be found in the Supporting Information.

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Keywords: alkynes · amines · enantioselectiveity · photochemistry · radical reactions

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[16] Hydrogen bonding of HN=S/MeN=S of sulfoximines with HO/HN has been observed in X-ray crystallographic structures. For examples, see: a) L. A. Paquette, D. N. Deaton, Y. Endo, M.-A. Poupart, *J. Org. Chem.* **1993**, *58*, 4262; b) J. F. K. Müller, M. Neuburger, M. Zehnder, *Helv. Chim. Acta* **1997**, *80*, 2182; c) H.-J. Gais, R. Hainz, H. Müller, P. R. Bruns, N. Giesen, G. Raabe, J. Runsink, S. Nienstedt, J. Decker, M. Schleusner, J. Hachtel, R. Loo, C.-W. Woo, P. Das, *Eur. J. Org. Chem.* **2000**, 3973; d) D. Leca, L. Fensterbank, E. Lacôte, M. Malacria, *Org. Lett.* **2002**, *4*, 4093; e) L. A. Paquette, F. Fabris, F. Gallou, S. Dong, *J. Org. Chem.* **2003**, *68*, 8625; f) N. El-Hachach, R. Gerke, M. Noltemeyer, L. Fitjer, *Tetrahedron* **2009**, *65*, 1040; g) R. Rodriguez, A.-S. Chapelon, C. Ollivier, M. Santelli, *Tetrahedron* **2009**, *65*, 7001.

[17] The N-acetyl group improved the enantioselectivity, presumably because higher acidity of the amide N–H in comparison to the carbamate N–H would further stabilize the transition state **G**.

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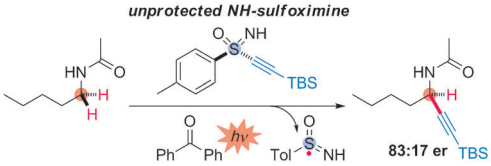

Without a trace: Enantioselective alkynylation of C(sp^3)–H bonds adjacent to a nitrogen atom has been achieved using only chiral *p*-tolyl *tert*-butyldimethylsilylethynyl sulfoximine and benzophenone under photo-irradiation conditions. The NH-unprotected sulfoximine group efficiently transmits its stereochemical information to the product and functions as a traceless chiral auxiliary.

Asymmetric Synthesis

*Masanori Nagatomo, Shun Yoshioka, Masayuki Inoue** _____ ▮▮▮▮–▮▮▮▮

Enantioselective Radical Alkynylation of C(sp^3)-H Bonds Using Sulfoximine as a Traceless Chiral Auxiliary

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