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Catalytic Amide−Base System of TMAF and N(TMS)$_3$ for Deprotonative Coupling of Benzylic C(sp^3)−H Bonds with Carbonyls

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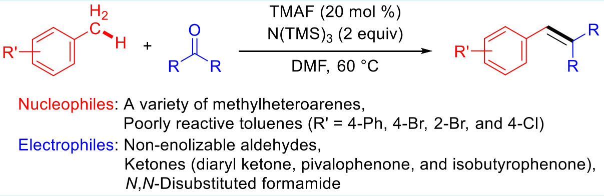
Supporting Information

ABSTRACT: This paper describes that an amide-base generated in situ from tetramethylammonium fluoride (TMAF) and N(TMS)$_3$ catalyzes the deprotonative coupling of benzylic C(sp^3)−H bonds with carbonyls to form stilbenes. A variety of methylheteroarenes (2-methylbenzothiophene, 2-methylbenzofuran, and 2-, 3-, or 4-methylpyridines) are used as nucleophiles. Application to enamine synthesis using DMF as an electrophile is also shown. The present system is effective for toluenes (4-phenyl-, 4-bromo-, 2-bromo-, and 4-chlorotoluenes) having low reactivity.



Brønsted base-induced deprotonative functionalization of C−H bonds, which is one of the most fundamental and important chemical transformations, is a powerful and straightforward method in organic chemistry.[1] In addition to the well-studied deprotonative functionalizations of C(sp^2)−H bonds of arenes and heteroarenes, functionalizations of benzylic C(sp^3)−H bonds are of great importance because of their potential application to the preparation of pharmaceuticals, agrochemicals, and electronic materials containing arenes and heteroarenes.[1e−g,2] For the deprotonation of benzylic C(sp^3)−H bonds, stoichiometric amounts of strong bases based on organometallic or dialkylamide reagents such as *n*-BuLi, *n*-BuLi/*t*-BuOK, *n*-BuLi/*t*-BuOK/TMP-H (2,2,6,6-tetramethylpiperidine), and LDA/*t*-BuOK, among others, are widely utilized.[1e−g,2,3] However, this approach has several drawbacks: (1) requirement of air- and moisture-sensitive reagents; (2) cryogenic conditions such as −78 °C to prevent warming of the reaction mixture by exothermic deprotonation and to minimize the occurrence of side reactions; (3) poor functional group tolerance; and (4) laborious two-step protocol involving deprotonation and subsequent coupling with an electrophile. Accordingly, the development of an efficient and practical system that facilitates the reaction of benzylic C(sp^3)−H bonds in various substrates is highly desirable.

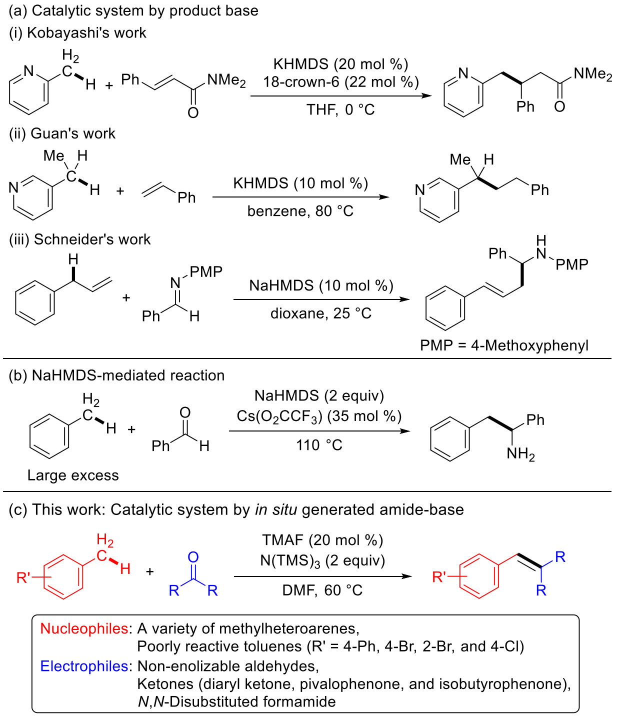


Figure 1. HMDS-amide-base-promoted deprotonative coupling reactions of benzylic C(sp^3)−H bonds.

Recently, KHMDS- or NaHMDS- (HMDS = hexamethyldisilazide),[4] weaker bases than organometallic or dialkylamide reagents, were found to catalyze or mediate the deprotonative functionalizations of benzylic C(sp^3)−H bonds with electrophiles (Figure 1).[5−7] The catalytic reactions were achieved by the Kobayashi, Guan, and Schneider groups, which include the coupling reactions of alkylazaarenes with *α*,*β*-unsaturated amides,[5a] alkylazaarenes with styrenes,[5b] and allylbenzenes with imines (Figure 1a).[5d] In these reactions, highly basic intermediates such as amide enolates, benzyl anions, or *N*-alkyl-*N*-methoxyphenylamide anions are generated, which likely contribute to efficient deprotonation of the benzylic C(sp^3)−H bonds in nucleophiles. This is referred to as a product base system.[6] An appropriate choice of electrophiles is critical for the catalytic reaction, and aldehyde or ketone carbonyls that generate less basic alkoxide intermediates are not employed.

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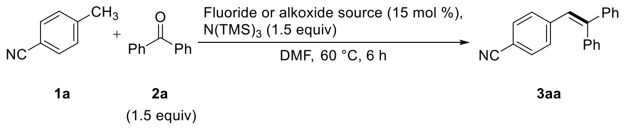
In addition, poorly reactive toluene derivatives are unsuitable for use as nucleophiles in such cases.[8] The Walsh group reported that the coupling reactions of the toluenes with aryl aldehydes, which proceed via the aldimine formation from the aldehyde, are mediated by a stoichiometric amount of NaHMDS with a catalytic amount of Cs(O_2CCF_3) (Figure 1b).[7,9] However, a large excess amount of toluenes (more than 30 equiv) was required for the reaction.

Our group has contributed to the development of deprotonative carbon−carbon bond formation by using an amide base generated in situ from a catalytic amount of fluoride or alkoxide salt and a stoichiometric amount of aminosilane.[10] The system was applied to the transformations of C(sp^2)−H bonds of heteroarenes such as benzothiophene, benzothiazole, benzofuran, and indole derivatives with carbonyls, as well as those of C(sp^3)−H bonds at the α-position of carbonyl compounds such as *N*,*N*-diethylacetamide and *t*-butyl acetate. As related studies, the transformations of acidic C(sp^3)−H bonds in trifluoromethane and difluoromethyl phenyl sulfone were also shown by the amide base;[11] however, the system has essentially not been applied to the transformations of the benzylic C(sp^3)−H bonds. In this paper, we describe in situ generated amide base catalyzed coupling reactions of benzylic C(sp^3)−H bonds with carbonyls to form stilbenes via deprotonative coupling and dehydration (Figure 1c).[12−14] In addition to various methylheteroarenes, poorly reactive toluene derivatives (4-phenyl-, 4-bromo-, 2-bromo-, and 4-chlorotoluenes) could be employed in this reaction.[15] The obtained stilbene is the core structural motif of functional and biologically active materials.[16] The present reaction is an alternative to the conventional Wittig or Heck olefination.[17−19] Enamine synthesis using DMF as an electrophile is also shown.

Initially, 4-cyanotoluene **1a**, which has a reactive benzylic proton (pK_a = 31, DMSO),[20] was examined in the coupling reaction with diphenyl benzophenone **2a** (Table 1). A variety of fluoride or alkoxide salts were screened in the presence of N(TMS)$_3$.[21] The reactions using alkoxide salts of NaOEt, NaO-*t*-Bu, KOEt, and KO-*t*-Bu afforded stilbene **3aa** in 67−76% NMR yields. Then the use of fluoride salts in the reaction was examined. In the presence of tetramethylammonium fluoride (TMAF), the reaction proceeded most efficiently to form **3aa** in 89% NMR yield. Increased amounts of TMAF (20 mol %), N(TMS)$_3$ (2 equiv), and **2a** (2 equiv) provided **3aa** in 88% isolated yield.[22−24]

Table 1. Optimization of the reaction of 1a and 2a[a]



entry	fluoride or alkoxide source	yield[b] (%)
1	NaOEt	73
2	NaO-*t*-Bu	67
3	KOEt	76
4	KO-*t*-Bu	76
5	CsF	75
6	TMAF	89
7	TMAF	quant (88)[c,d]
8	TBAT[e]	77

[a]Reactions were conducted on a 0.2 mmol scale. [b]Yields were determined by ^{1}H NMR analysis. [c]TMAF (20 mol %), N(TMS)$_3$ (2 equiv), and **2a** (2 equiv) were used. [d]Yield in parentheses denotes isolated yield. [e]Tetrabutylammonium difluorotriphenylsilicate.

The optimized conditions were applied to the reaction of methylheteroarenes **4a−e** (Figure 2). 2-Methylbenzothiophene **4a** reacted with **2a** to afford stilbene **5aa** in 98% yield. Tricyclic ketones such as xanthone **2b**, thioxanthone **2c**, and dibenzosuberenone **2d** gave the corresponding stilbenes **5ab**, **5ac**, and **5ad** in 87%, 90%, and 63% yields, respectively. Then the reactions of alkyl aryl ketones **2e** and **2f** were investigated. Sterically hindered pivalophenone **2e** underwent the coupling reaction to furnish **5ae** in 90% yield. Isobutyrophenone **2f**, bearing a C(sp^3)−H bond at the α-position of carbonyl, was also coupled with **4a** to form a *Z*/*E* mixture of **5af-1** in 32% yield (*Z*/*E* = 90:10) along with the formation of **5af-2** in 23% yield.[25,26] The reactions of 2-methylbenzofuran **4b** with **2a**, 4,4′-dimethoxybenzophenone **2g**, 4,4′-difluorobenzophenone **2h**, and 4,4′-dichlorobenzophenone **2i** gave the corresponding coupling products **5ba**, **5bg**, **5bh**, and **5bi** in 97%, 87%, 77%, and 85% yields, respectively. Use of pivalaldehyde **2j** and 4-(dimethylamino)benzaldehyde **2k** as electrophiles furnished **5bj** and **5bk** in 87% and 63% yields, respectively. Next, methylpyridines **4c−e** were employed in the reaction. 4- and 2-methylpyridines **4c** and **4d**, with pK_a values of 32.2 and 34[21] (THF) corresponding to the benzylic positions, respectively,

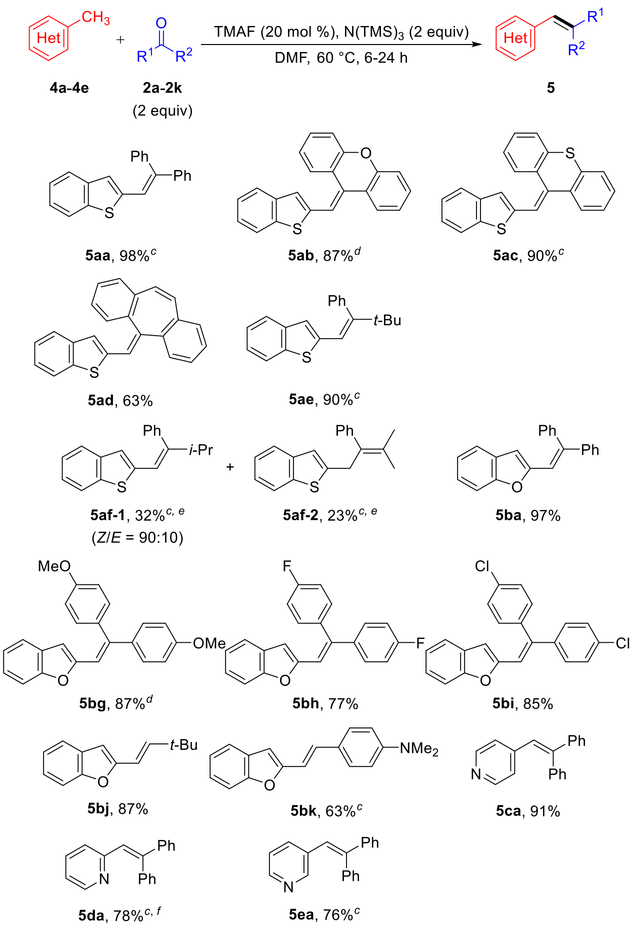


Figure 2. Reactions of methylheteroarenes and carbonyls. (a) Reactions were conducted on a 0.2 mmol scale. (b) Isolated yields. (c) TMAF (30 mol %) and N(TMS)$_3$ (3 equiv) were used. (d) Reaction was conducted at 80 °C. (e) DMI was used as a solvent. (f) Reaction was conducted at 40 °C.

provided coupling products **5ca** and **5da** in 91% and 78% yields. Note that 3-methylpyridine **4e** having a larger pK_a of 37.7[21] (THF) also coupled with **2a** to give **5ea** in 76% yield.

The scale-up of the current reaction was performed (Scheme S3). The reaction of **4a** (5.0 mmol) with **2b** afforded 1.34 g of **5ab** (4.11 mmol) in 82% yield.

This type of transformation can be employed for the synthesis of enamines using DMF as an electrophile (Figure 3). Methylheteroarenes **4a**, **4b**, and **4c** were employed to furnish the desired enamines in 95%, 96%, and 66% yields, respectively. *N*-Methylformanilide **7** was also used as an electrophile, which resulted in the formation of **8a** in 38% yield.

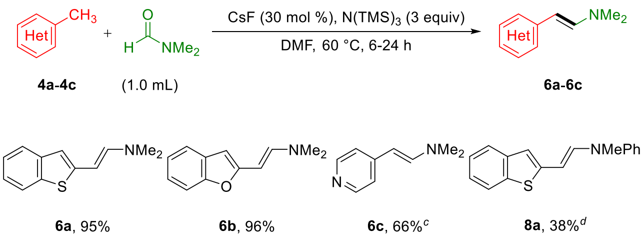


Figure 3. Enamine synthesis with DMF or *N*-methylformanilide as an electrophile. (a) Reactions were conducted on a 0.2 mmol scale. (b) Isolated yields. (c) TMAF (20 mol %) and N(TMS)$_3$ (2.0 equiv) were used. (d) TMAF (30 mol %) was used. *N*-Methylformanilide **7** (2.0 equiv) was used as an electrophile. DMI (1.0 mL) was used as a solvent.

We next examined whether toluene derivatives having a high pK_a are suitable substrates for our protocol (Figure 4).[15] 4-Phenyltoluene **1b**, which has a pK_a value of 38.57[27] (THF) corresponding to the benzylic position, reacted with **2b** in the presence of TMAF (30 mol %) and N(TMS)$_3$ (3 equiv) to provide **3bb** in 80% yield after treatment with HCl. Coupling reactions of **1b** with **2c** and **2d** also took place to form **3bc** and **3bd** in 90% and 80% yields, respectively. Then the reaction of 4-bromotoluene **1c** was examined. In the reaction using *n*-BuLi/*t*-BuOK/TMP-H, debromination occurs as a side reaction.[28] To our delight, with our system, wherein CsF was used as a fluoride salt, the bromine moiety was tolerated to furnish the corresponding product **3ca** in 72% yield (Table S1).[29,30] The reactions of **1c** with **2b** and **2c** also proceeded to form the corresponding stilbenes **3cb** and **3cc** in 88% and 80% yields, respectively.[31,32] Uses of 2-bromotoluene **1d** and 4-chlorotoluene **1e** in the reactions with **2b** resulted in the formations of **3db** and **3eb** in 70% and 62% yields, respectively. In this system, toluene was also employed in the reactions with **2a** and **2b**; however, no desired products were obtained (results not shown).

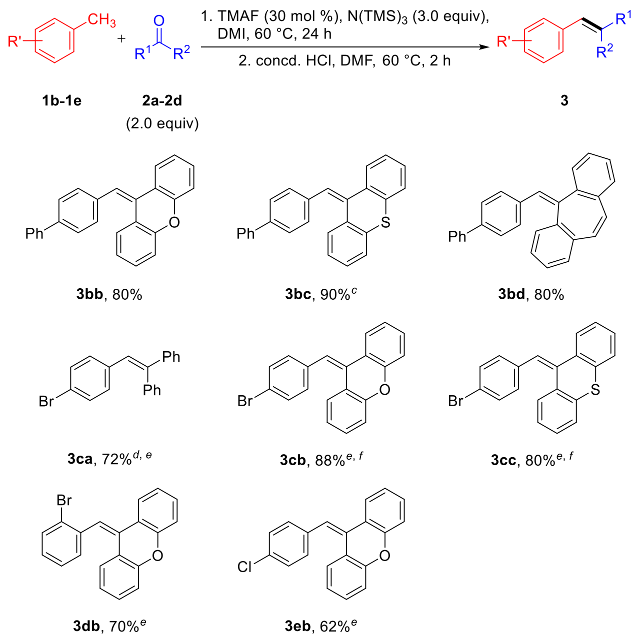
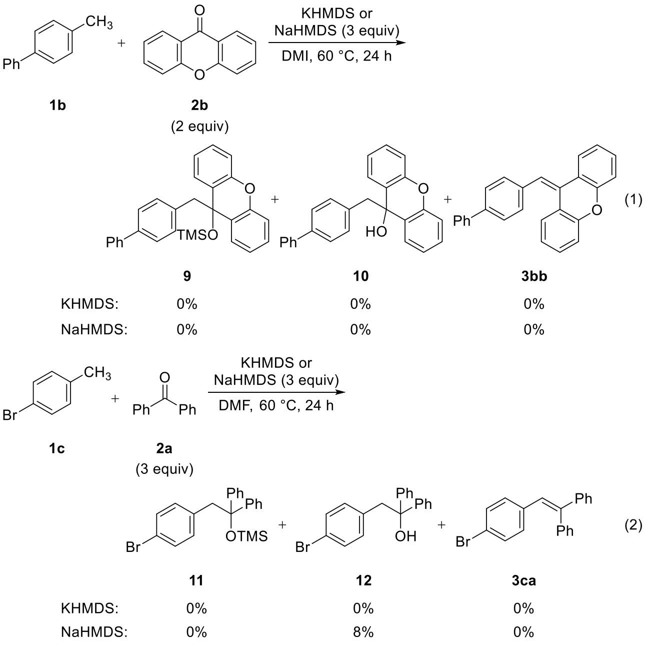


Figure 4. Reactions of poorly reactive toluenes with carbonyls. (a) Reactions were conducted on a 0.2 mmol scale. (b) Isolated yields. (c) DMPU was used as a solvent. (d) CsF (30 mol %), N(TMS)$_3$ (3.0 equiv), and **2a** (3.0 equiv) were used. (e) DMF was used as a solvent. (f) Reaction was conducted at 80 °C.

Reactions with stoichiometric amounts of NaHMDS and KHMDS were carried out for comparison with the catalytic system of the amide base generated in situ.[33] The use of 3 equiv of NaHMDS or KHMDS in the reactions of **1b** and **1c** afforded much lower yields of the coupling products than those observed with our catalytic system (Figure 4; Scheme 1), which revealed the merit of the present protocol. It should also be noted that the amide base generated in situ from KOEt/N(TMS)$_3$ gave the products (**11**, **12**, and **3ca**) in a higher yield than did the same cation of KHMDS (Table S1; Scheme 1 (2)). Such a trend was also observed in the reactions using NaOEt/N(TMS)$_3$ and NaHMDS (Table S1; Scheme 1 (2)). From these results, the key features of the current system can be established: that is, the ammonium or alkali metal cation can control the reactivity of the amide base, and the strong O−Si bond formation is a driving force for the reaction.

Scheme 1. Reactions of 1b and 1c with Carbonyls in the Presence of KHMDS or NaHMDS[a,b]



[a]Reactions were conducted on a 0.2 mmol scale. [b]Yields were determined by ^{1}H NMR analysis.

The mechanism of the transformation is depicted in Figure 5. Amide base **A** generated in situ from TMAF and N(TMS)$_3$ triggers the deprotonation of the benzylic C(sp^3)−H bond of **1**.[11a] The resulting benzylic anion **B** adds to **2** to give alkoxide **C**.

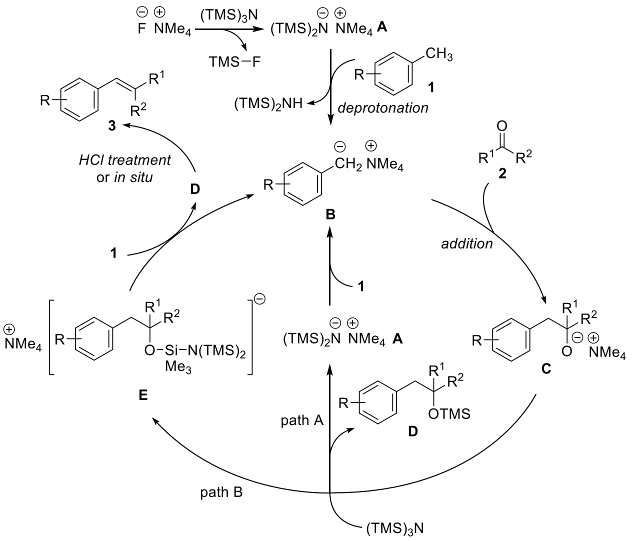


Figure 5. Proposed mechanism of the in situ generated amide base promoted deprotonative coupling to form stilbenes.

Then **C** reacts with $N(TMS)_3$ to provide silyl ether **D** and regenerate **A** (path A). Alternatively, the silicate species **E** formed by the coordination of **C** onto the silicon atom of $N(TMS)_3$ might induce deprotonation (path B).[11a] At this stage, further mechanistic studies are required to reveal which path is more plausible. When **1a** or **4a−e** were used as a nucleophile, the dehydrated products of stilbenes **3** were obtained after the reaction. In such cases, elimination of trimethysiloxide is considered to occur by the amide or siloxide base with the formation of $NH(TMS)_2$ or trimethylsilanol. The eliminated siloxide base reacts with $N(TMS)_3$ to form an amide base and $(TMS)_2O$, as noted in our previous study.[10c] In the reactions of **1b−e**, silyl ethers corresponding to **D** were formed after the reaction. HCl treatment was required to convert **D** into stilbenes.

In summary, we developed a novel deprotonative coupling reaction of benzylic $C(sp^3)$−H bonds with carbonyls to form stilbenes. The system was applicable to the transformation of various methylheteroarenes as well as poorly reactive toluenes. The present catalytic system was more effective than conventional amide bases (NaHMDS and KHMDS). We are currently working to apply this catalytic system to the reactions of other poorly reactive C−H bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00550.

> Experimental details of synthetic procedures, reactions of cyanotoluenes and electrophiles (Scheme S1), stilbene formation using wet DMF as a solvent (Scheme S2), scale-up of the reaction of **4a** with **2b** (Scheme S3), optimization of the reaction of **1c** and **2a** (Table S1), spectra data for obtained products, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For examples of reviews, see: (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (c) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794. (d) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. *Chem. Rev.* **2017**, *117*, 9302. (e) Florio, S.; Salomone, A. *Synthesis* **2016**, *48*, 1993. (f) Tilly, D.; Magolan, J.; Mortier, J. *Chem. - Eur. J.* **2012**, *18*, 3804. (g) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (h) Kobayashi, S.; Matsubara, R. *Chem. - Eur. J.* **2009**, *15*, 10694. (i) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760.

(2) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

(3) (a) Schlosser, M.; Maccaroni, P.; Marzi, E. *Tetrahedron* **1998**, *54*, 2763. (b) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, *2000*, 1115. (c) Fleming, P.; O'Shea, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 1698.

(4) Mulvey, R. E.; Robertson, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 11470.

(5) (a) Suzuki, H.; Igarashi, R.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 4520. (b) Zhai, D.-D.; Zhang, X.-Y.; Liu, Y.-F.; Zheng, L.; Guan, B.-T. *Angew. Chem., Int. Ed.* **2018**, *57*, 1650. The Guan group also reported the potassium zincate complex of $KZn(HMDS)_2Bn$ catalyzed coupling reaction of diarylmethanes with stylenes; see: (c) Liu, Y.-F.; Zhai, D.-D.; Zhang, X.-Y.; Guan, B.-T. *Angew. Chem., Int. Ed.* **2018**, *57*, 8245. (d) Bao, W.; Kossen, H.; Schneider, U. *J. Am. Chem. Soc.* **2017**, *139*, 4362.

(6) Yamashita, Y.; Kobayashi, S. *Chem. - Eur. J.* **2018**, *24*, 10.

(7) (a) Wang, Z.; Zheng, Z.; Xu, X.; Mao, J.; Walsh, P. J. *Nat. Commun.* **2018**, *9*, 3365. Also see: (b) Sha, S.-C.; Tcyrulnikov, S.; Li, M.; Hu, B.; Fu, Y.; Kozlowski, M. C.; Walsh, P. J. *J. Am. Chem. Soc.* **2018**, *140*, 12415.

(8) Several catalytic deprotonative functionalizations of benzylic $C(sp^3)$−H bonds of poorly reactive toluenes with olefins or imines were achieved by the product base system, which were required to use strong bases as follows. Alkali metals (Na and K): (a) Pines, H.; Vesely, J. A.; Ipatieff, V. N. *J. Am. Chem. Soc.* **1955**, *77*, 554. (b) Pines, H. *Acc. Chem. Res.* **1974**, *7*, 155. n-BuLi/$LiK(OCH_2CH_2NMe_2)_2$/$Mg(OCH_2CH_2OEt)_2$: (c) Steele, B. R.; Screttas, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 2391. *t*-BuOK/LiTMP: (d) Yamashita, Y.; Suzuki, H.; Sato, I.; Hirata, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2018**, *57*, 6896. KCH_2SiMe_3/*N,N,N′,N″,N″*-pentamethyldiethylenetriamine: (e) Sato, I.; Yamashita, Y.; Kobayashi, S. *Synthesis* **2019**, *51*, 240. Also see the reports using the yttrium alkyl complex: (f) Oyamada, J.; Hou, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12828.

(9) As a related study, the Mulvey group reported that a stoichiometric amount of $KHMDS/Zn(HMDS)_2$ induced the deprotonations of benzylic $C(sp^3)$−H bonds of toluene, *m*-xylene, and mesitylene under heating conditions. See: Clegg, W.; Forbes, G. C.; Kennedy, A. R.; Mulvey, R. E.; Liddle, S. T. *Chem. Commun.* **2003**, 406.

(10) (a) Inamoto, K.; Okawa, H.; Taneda, H.; Sato, M.; Hirono, Y.; Yonemoto, M.; Kikkawa, S.; Kondo, Y. *Chem. Commun.* **2012**, *48*, 9771. (b) Inamoto, K.; Okawa, H.; Kikkawa, S.; Kondo, Y. *Tetrahedron* **2014**, *70*, 7917. (c) Taneda, H.; Inamoto, K.; Kondo, Y. *Chem. Commun.* **2014**, *50*, 6523. (d) Shigeno, M.; Fujii, Y.; Kajima, A.; Nozawa-Kumada, K.; Kondo, Y. *Org. Process Res. Dev.* **2018**, DOI: 10.1021/acs.oprd.8b00247. Also see: (e) Shigeno, M.; Kai, Y.; Yamada, T.; Hayashi, K.; Nozawa-Kumada, K.; Denneval, C.; Kondo, Y. *Asian J. Org. Chem.* **2018**, *7*, 2082.

(11) (a) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848. (b) Hu, M.; Gao, B.; Ni, C.; Zhang, L.; Hu, J. *J. Fluorine Chem.* **2013**, *155*, 52. Also see: (c) Okusu, S.; Hirano, K.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2015**, *4*, 581. (d) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J. *Chem. - Eur. J.* **2014**, *20*, 7803.

(12) Intermolecular coupling reactions of benzylic C(sp^3)−H bonds with carbonyls to form C−C bonds were achieved by several methodologies of Lewis acid catalysis of Cu(OTf)$_2$,[12a] Yb(OTf)$_3$,[12b] LiNTf$_2$,[12c] and Zn(OTf)$_2$,[12d] Brønsted-acid catalyzed or mediated reactions of TfOH,[12e] AcOH,[12f] TsOH,[12g] and acid ionic liquid,[12h] transition-metal catalysis of [Cp*Ru(η^6-toluene)][NHTs][12i] and Fe(OAc)$_2$,[12j] other catalysis of iodine (I$_2$),[12k] TBAF,[12l] and β-cyclodextrin,[12m] and catalyst-free reaction.[12n] In the reactions, relatively reactive electron-poor alkylazaarenes such as 2- or 4-methyl pyridine derivatives, 2-methyl quinoline derivatives, and 1-methylisoquinoline were used, and toluene derivatives were not except the reaction using Ru catalyst.[12i] As a coupling partner, electrophilic carbonyls of α-trifluoromethyl ketones, α-ketoamides, ethyl glyoxylate, and isatins, and aliphatic or aromatic aldehydes were used, and electronically nonactivated ketones were not. See: (a) Jin, J.-J.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M.; Fossey, J. S. *RSC Adv.* **2012**, *2*, 5968. (b) Graves, V. B.; Shaikh, A. *Tetrahedron Lett.* **2013**, *54*, 695. (c) Mao, D.; Hong, G.; Wu, S.; Liu, X.; Yu, J.; Wang, L. *Eur. J. Org. Chem.* **2014**, *2014*, 3009. (d) Muthukumar, A.; Sekar, G. *Org. Biomol. Chem.* **2017**, *15*, 691. (e) Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.* **2012**, *14*, 676. (f) Wang, F.-F.; Luo, C.-P.; Wang, Y.; Deng, G.; Yang, L. *Org. Biomol. Chem.* **2012**, *10*, 8605. (g) Jin, J.-J.; Wang, D.-C.; Niu, H.-Y.; Wu, S.; Qu, G.-R.; Zhang, Z.-B.; Guo, H.-M. *Tetrahedron* **2013**, *69*, 6579. (h) Zhang, X.-Y.; Dong, D.-Q.; Yue, T.; Hao, S.-H.; Wang, Z.-L. *Tetrahedron Lett.* **2014**, *55*, 5462. (i) Takemoto, S.; Shibata, E.; Nakajima, M.; Yumoto, Y.; Shimamoto, M.; Matsuzaka, H. *J. Am. Chem. Soc.* **2016**, *138*, 14836. (j) Jiang, K.; Pi, D.; Zhou, H.; Liu, S.; Zou, K. *Tetrahedron* **2014**, *70*, 3056. (k) Vuppalapati, S. V. N.; Lee, Y. R. *Tetrahedron* **2012**, *68*, 8286. (l) Kumari, K.; Allam, B. K.; Singh, K. N. *RSC Adv.* **2014**, *4*, 19789. (m) Kumar, A.; Dutt Shukla, R. *Green Chem.* **2015**, *17*, 848. (n) Xu, L.; Shao, Z.; Wang, L.; Zhao, H.; Xiao, J. *Tetrahedron Lett.* **2014**, *55*, 6856. Also see the reviews: (o) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (p) Vanjari, R.; Singh, K. N. *Chem. Soc. Rev.* **2015**, *44*, 8062.

(13) Chiba and co-workers demonstrated that a stoichiometric amount of NaH−LiI composite proceeded the directed metalation at the benzylic position and the intramolecular addition to the amide carbonyls. (a) Huang, Y.; Chan, G. H.; Chiba, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 6544. A similar type of reaction proceeds by using LDA. (b) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710.

(14) A stoichiometric amount of alkali metal fluoride (CsF or KF)−Al$_2$O$_3$ composites or alkoxide bases promote deprotonative coupling reactions of relatively reactive benzylic C(sp^3)−H bonds of toluenes having an electron-withdrawing group, electron-deficient methyl azaarenes, or cyclic diarylmethanes (fluorene, xanthene, and thioxanthene) with aldehydes. (a) Hellwinkel, D.; Göke, K.; Karle, R. *Synthesis* **1994**, *1994*, 973. (b) Rangnekar, D. W.; Lokhande, S. B. *Indian J. Chem.* **1986**, *25*, 485. (c) Takahashi, K.; Okamoto, T.; Yamada, K.; Iida, H. *Synthesis* **1977**, *1977*, 58. (d) Kaiser, E. M.; Hartzell, S. L. *J. Org. Chem.* **1977**, *42*, 2951. (e) Luo, F.-T.; Chen, C.-H. *Heterocycles* **2001**, *55*, 1663.

(15) *n*-BuLi was previously used for the deprotonative coupling reactions of poorly reactive toluenes with diarylketones. (a) Suzuki, T.; Sakano, Y.; Iwai, T.; Iwashita, S.; Miura, Y.; Katoono, R.; Kawai, H.; Fujiwara, K.; Tsuji, Y.; Fukushima, T. *Chem. - Eur. J.* **2013**, *19*, 117. (b) Yamaguchi, T.; Yamamoto, Y.; Fujiwara, Y.; Tanimoto, Y. *Org. Lett.* **2005**, *7*, 2739.

(16) Likhtenshtein, G. *Stilbenes: Applications in Chemistry, Life Sciences and Materials Science*; Wiley-VCH: Weinheim, 2010.

(17) (a) Campbell, T. W.; McDonald, R. N. *J. Org. Chem.* **1959**, *24*, 1246. (b) Xie, Z.; Yang, B.; Li, F.; Cheng, G.; Liu, L.; Yang, G.; Xu, H.; Ye, L.; Hanif, M.; Liu, S.; Ma, D.; Ma, Y. *J. Am. Chem. Soc.* **2005**, *127*, 14152.

(18) (a) Kumpf, J.; Bunz, U. H. F. *Chem. - Eur. J.* **2012**, *18*, 8921. (b) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692.

(19) The reactions of benzylic C(sp^3)−H bonds with aldimines afford the stilbenes in the presence of a stoichiometric amount of alkoxide bases (Siegrist reaction), in which ketoimines are not employed. (a) Siegrist, A. E. *Helv. Chim. Acta* **1967**, *50*, 906. (b) Siegrist, A. E.; Liechti, P.; Meyer, H. R.; Weber, K. *Helv. Chim. Acta* **1969**, *52*, 2521. (c) Bléger, D.; Kreher, D.; Mathevet, F.; Attias, A.-J.; Schull, G.; Huard, A.; Douillard, L.; Fiorini-Debuischert, C.; Charra, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7404. (d) Meier, H.; Lifka, T.; Stalmach, U.; Oehlhof, A.; Prehl, S. *Eur. J. Org. Chem.* **2008**, *2008*, 1568.

(20) Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817.

(21) The pK_a value of HN(TMS)$_2$, a conjugate acid of the amide base employed in this study, is 25.8 (THF). Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. pK_a values of methylpyridines **4c**−**e** are also noted in this literature.

(22) The reactions performed in the absence of TMAF (20 mol %) or N(TMS)$_3$ (2 equiv) exhibited no product formation, highlighting the necessity of both TMAF and N(TMS)$_3$.

(23) Compound **1a** also affords the stilbenes in the reaction with 4-(dimethylamino)benzaldehyde and benzaldehyde in 87% and 70% yields, respectively. The former product was obtained as an *E*/*Z* isomeric mixture (*E*/*Z* = 93:7). 2-Cyanotoluene also coupled with **2a** to yield the product in 89% yield (Scheme S1).

(24) In the present study, anhydrous DMF was used as a solvent. However, it was confirmed that, even using wet DMF, the reactions of **1a** and **4a** with **2a** proceeded to give the corresponding products in high yields of 87% and 94% yields, respectively (Scheme S2).

(25) 2-Ethylbenzothiophene was employed in the reaction with **2a**, however, which resulted in no desired product formation (results not shown).

(26) Use of dicyclohexyl ketone in the reaction with **4a** did not provide the coupling product (results not shown).

(27) Bors, D. A.; Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6975.

(28) Das, M.; O'Shea, D. F. *Tetrahedron* **2013**, *69*, 6448.

(29) In the reaction of **1c** and **2a**, CsF was found to be effective compared with TMAF or alkoxide salts (Table S1).

(30) Walsh and co-workers also recently demonstrated that the reactions of 2-bromotoluene **1d** (large excess) and aldimines proceed with the tolerance of the bromine moiety by using a stoichiometric amount of NaHMDS and a catalytic amount of Cs(O$_2$CCF$_3$). See ref 7a.

(31) When CsF (30 mol %) was used instead of TMAF, **3cb** and **3cc** were formed in NMR yields of 69% and 75%, respectively.

(32) The reactions of **1c** with **2f** and **2j** were conducted but did not form the coupling products (results not shown).

(33) For recent examples of deprotonative functionalizations using a stoichiometric amount of NaHMDS or KHMDS, see: (a) Wang, D.-Y.; Yang, Z.-K.; Wang, C.; Zhang, A.; Uchiyama, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 3641. (b) Ogawa, N.; Yamaoka, Y.; Takikawa, H.; Tsubaki, K.; Takasu, K. *J. Org. Chem.* **2018**, *83*, 7994. (c) Costil, R.; Dale, H. J. A.; Fey, N.; Whitcombe, G.; Matlock, J. V.; Clayden, J. *Angew. Chem., Int. Ed.* **2017**, *56*, 12533. (d) Diaz Ropero, B. P. F.; Elsegood, M. R. J.; Fairley, G.; Pritchard, G. J.; Weaver, G. W. *Eur. J. Org. Chem.* **2016**, *2016*, 5238. (e) Bhanuchandra, M.; Yorimitsu, H.; Osuka, A. *Org. Lett.* **2016**, *18*, 384.