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Catalytic amide base system generated *in situ* for 1,3-diene formation from allylbenzenes and carbonyls†

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The amide base generated *in situ* from tetramethylammonium fluoride and N(TMS)$_3$ catalyzes the synthesis of 1,3-diene from an allylbenzene and carbonyl compound. The system is applicable to the transformations of a variety of allylbenzenes with functional groups (halogen, methyl, phenyl, methoxy, dimethylamino, ester, and amide moieties). Acyclic and cyclic diaryl ketones, pivalophenone, pivalaldehyde, and isobutyrophenone are used as coupling partners. The role of *trans* β-methyl stilbenes in product formation is also elucidated.

The establishment of the synthetic methodologies of 1,3-dienes has gained considerable attention among organic chemists owing to the presence of these molecules in biologically active compounds and natural products and their use as synthetically potent modules in organic synthesis (Diels–Alder reaction and hydrofunctionalization).[1] Wittig, Horner–Wadsworth–Emmons, Julia–Kocienski, and Peterson olefinations are traditional and reliable protocols for the synthesis of 1,3-dienes, in which functionalized allylic substrates, such as allylphosphonium salts, allyl phosphonates, allyl sulfones, and allyl silanes are employed for the coupling reactions with carbonyls.[1–4] Non-functionalized allylbenzenes are easily available and thus, their direct conversion to 1,3-dienes is attractive. However, such examples are still limited. For example, Gong *et al.* reported that in the presence of Pd and Cr catalysts combined with benzoquinone, the coupling reactions of allylbenzenes with α-diazo esters afford the 1,3-dienoates (Fig. 1, i).[5] Jiang *et al.* reported that Pd catalyzes the allylic C–H olefinations of allylbenzenes with sulfoxonium ylides to form 1,3-dienones (Fig. 1, ii).[6] Recently, deprotonative functionalizations of allylbenzenes have been studied using catalytic and stoichiometric amounts of hexamethyldisilazide bases (HMDS = hexamethyldisilazide; Fig. 1b).[7–11] These bases compensate for the limited substrate scope and functional group tolerance posed by conventional reactions using strong Brønsted bases such as *n*-BuLi, *sec*-BuLi, Grignard reagents, and NaNH$_2$.[12] Schneider *et al.* revealed that a catalytic amount of NaHMDS promotes the deprotonative coupling of allylbenzenes with aldimines (Fig. 1, iii), while Walsh *et al.* reported that LiHMDS is an appropriate base for the Pd-catalyzed arylations of allylbenzenes (Fig. 1, iv). However, to date, deprotonative reactions

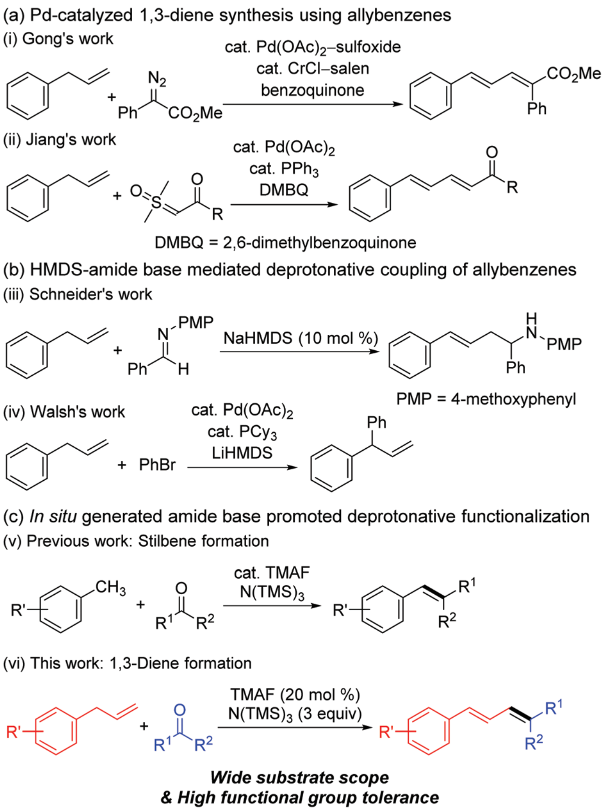

Fig. 1 1,3-Diene syntheses of allylbenzenes and deprotonative functionalizations related to this study.

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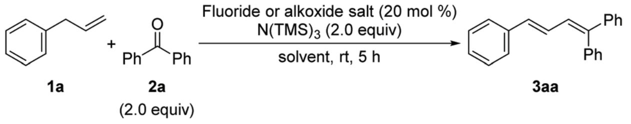
using HMDS-amide base have not been applied to the synthesis of 1,3-dienes.[13]

We have previously studied the deprotonative functionalizations of C–H pronucleophiles using HMDS-amide base generated *in situ* from a catalytic amount of fluoride salt and a stoichiometric amount of aminosilane.[14,15] In addition to the reactions of heteroarenes, acetates, and terminal alkynes used as a pronucleophile, stilbene formation of methyl(hetero)arenes with carbonyl compounds was recently achieved (Fig. 1, v).[14e] In this study, we established that the system is effective for the deprotonative coupling of allylbenzenes with carbonyls to afford 1,3-dienes (Fig. 1, vi). The reaction proceeds at nearby ambient temperature and displays a high functional group tolerance (methyl, phenyl, halogen, methoxy, dimethylamino, 1,3-benzodioxole, ester, and amide moieties) in allylbenzenes. Carbonyl electrophiles such as acyclic and cyclic diaryl ketones (xanthone, thioxanthone, fluorenone, and suberenone), pivalophenone, pivalaldehyde, and isobutyrophenone were employed in the reaction. The system was also applied to the conversions of *trans*-β-methylstilenes.

Initially, the 1,3-diene formation process was examined using allylbenzene **1a** and benzophenone **2a** as model substrates (Table 1). The effects of fluoride and alkoxide salts were investigated in *N*,*N*-dimethylformamide (DMF). The results revealed that tetramethylammonium fluoride (TMAF) was the most effective, affording **3aa** in 90% yield (entries 1–7). Solvents other than DMF were also tested (entries 8–12): 1,3-dimethyl-2-imidazolidinone (DMI) afforded the product in 73% yield, while *N*,*N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), and toluene were ineffective. The use of $N(TMS)_3$ (3 equiv.) resulted in the formation of **3aa** in 90% isolated yield (entry 13).[16]

Table 1 Optimization of 1,3-diene formation of **1a** with **2a** [a]



Entry	Fluoride or alkoxide source	Solvent	Yield[b] (%)
1	KF	DMF	0
2	RbF	DMF	0
3	CsF	DMF	48
4	NaOMe	DMF	61
5	NaO-*t*-Bu	DMF	56
6	KO-*t*-Bu	DMF	81
7	TMAF	DMF	90 (88)[c]
8	TMAF	DMI	73
9	TMAF	DMA	22
10	TMAF	DMSO	0
11	TMAF	THF	0
12	TMAF	Toluene	0
13	TMAF	DMF	99 (90)[c–e]

[a] Reactions were conducted at 0.2 mmol scale. [b] Yields were determined by ^{1}H-NMR analysis. [c] Yield in parentheses denotes the isolated yield. [d] $N(TMS)_3$ (3 equiv.) was used. [e] *E*/*Z* ratio was determined to be >30 : 1 by ^{1}H-NMR analysis of the isolated product.

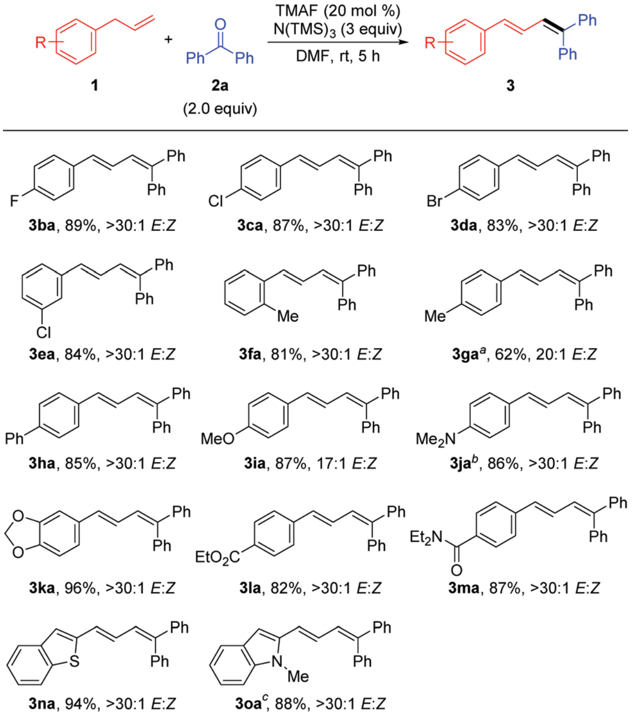


Fig. 2 Scope of allyl(hetero)arenes **1** for the 1,3-diene formation with **2a**. Reactions were conducted at 0.2 mmol scale. Isolated yields. *E*/*Z* ratios were determined by ^{1}H-NMR analysis of the isolated product. [a] **2a** (1.1 equiv.) was used. [b] Product was isolated after treatment with HCl. [c] Reaction was conducted with TMAF (30 mol%) in DMI.

With the optimized conditions in hand, the scope of the allylbenzene pronucleophiles was next surveyed (Fig. 2). The halogen atoms (F, Cl, and Br) on the phenyl group were well-tolerated to afford the coupling products **3ba–3ea** in high yields. Allylbenzenes **1f** and **1g**, which bear methyl groups at the *ortho*- and *para*-positions, respectively, afforded the products in 81% and 62% respective yields, while phenyl-substituted **1h** afforded **3ha** in 85% yield. The reactions of substrates comprising electron-donating methoxy and dimethylamino substituents also proceeded smoothly to afford the products in 87% and 86% yields, respectively.[17] Safrole **1k** underwent the reaction to yield the product **3ka** in 96% yield. The electrophilic ester and amide moieties were compatible with the reactions to provide the desired products **3la** and **3ma**. 2-Allylbenzothiophene **1n** and 2-allyl-1-methylindole **1o** were suitable and furnished the corresponding products in 94% and 88% yields, respectively. 1-Octene and 1,4-pentadiene were also tested in the reactions, however, no desired products were formed (results not shown).

The proposed 1,3-diene formation of **1a** was next performed with a variety of carbonyl compounds (Fig. 3). Thus, diaryl ketones **2b–2d** possessing F, Cl, and methoxy substituents were subjected to the reaction, providing the respective 1,3-dienes in 79%, 71%, and 92% yields, respectively. When xanthone **2e** and thioxanthone **2f** were used as the electrophile, the desired products **3ae** and **3af** were produced in the

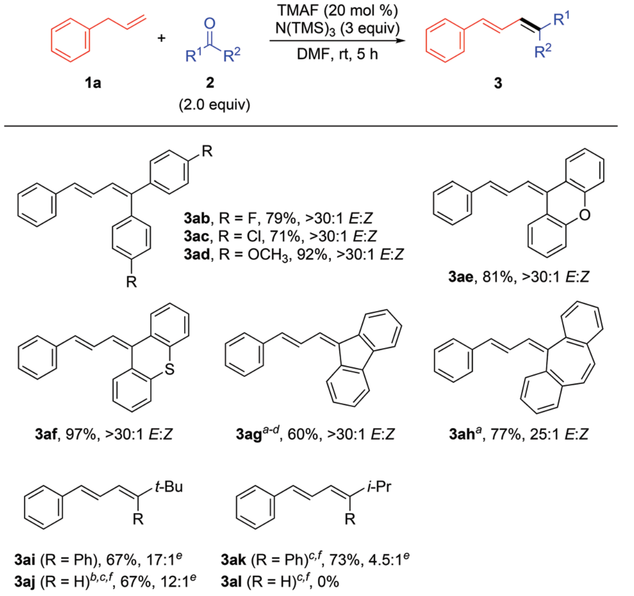
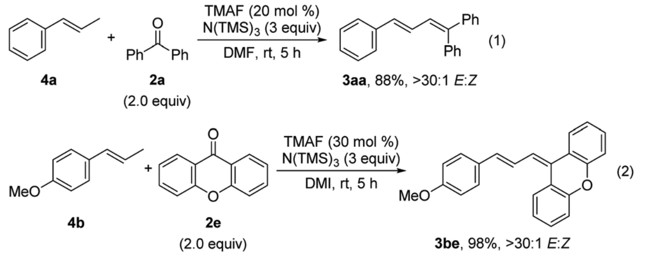


Fig. 3 Scope of carbonyl compounds **2**. Reactions were conducted at 0.2 mmol scale. Isolated yields. *E*/*Z* ratios were determined by ^{1}H-NMR analysis of the isolated product. [a] Products were isolated after treatment with HCl. [b] TMAF (30 mol%) was used. [c] DMI was used as a solvent. [d] Reaction was conducted at 40 °C. [e] Ratios of major isomer/minor isomers were determined by ^{1}H-NMR analysis of the isolated product. [f] Reaction was conducted at 60 °C.

respective yields of 81% and 97%. 9-Fluorenone **2g** and dibenzosuberenone **2h** also reacted with **1a** to afford **3ag** and **3ah**, respectively. Subsequently, *tert*-butyl phenyl ketone **2i** was applied to the reaction and the 1,3-diene **3ai** was furnished in 67% yield.[18] Pivaladehyde **2j** was also used in the reaction to form **3aj** in 67% yield. As enolizable carbonyl compounds, isobutyrophenone **2k** and isobutyraldehyde **2l** were tested; the former gave the target product in 73% yield, while the latter gave neither 1,3-diene nor silyl ether product.† [19]

We further examined the reactions of *trans* β-methyl stilbenes **4**, which are less reactive than the corresponding allyl arenes (Scheme 1).[20] Fortunately, the reactions of **4a** and **4b** with carbonyls proceeded smoothly to afford the products in 88% and 98% yields, respectively.[21]



Scheme 1 Reactions of *trans* β-methyl stilbenes **4**. Reactions were conducted at 0.2 mmol scale. Isolated yields. *E*/*Z* ratios were determined by ^{1}H-NMR analysis of the isolated product.

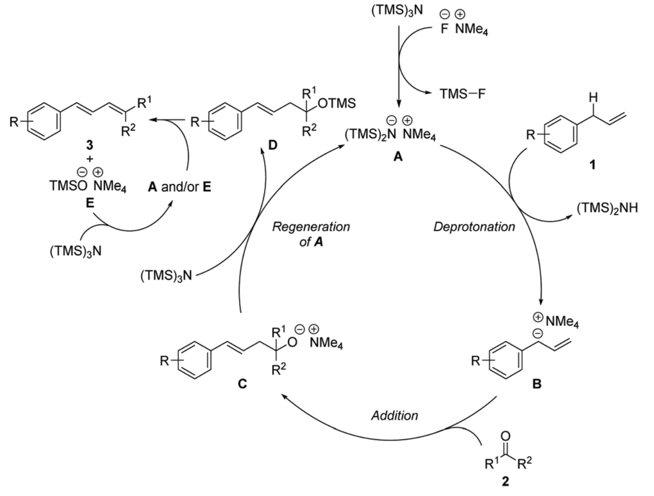


Fig. 4 Proposed mechanism of the present 1,3-diene formation.

The proposed mechanism for the 1,3-diene formation process is portrayed in Fig. 4. Amide base **A**, which is initially generated from TMAF and N(TMS)$_3$, induces the deprotonation of **1** to afford allyl anion **B**.[15a] Next, **B** reacts with **2** to form alkoxide **C**, which subsequently produces silyl ether **D** with the concomitant formation of **A**. The conversion of **D** to **3** is assisted by **A** and/or siloxide **E**.[22]

Conclusions

In summary, we demonstrated that the catalytic amide system using TMAF and N(TMS)$_3$ can be employed for the preparation of 1,3-dienes from allylbenzenes and carbonyls. The current system displayed a broad substrate scope for both reactants. β-Methyl stilbenes were also found to be relevant as a pronucleophile.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 In the general procedure of this study, after quenching the reaction with H_2O, the mixture was stirred at room temperature for 1 h, analogously to the procedure of our previous report of stilbene synthesis[14e] (see ESI†). However, it was confirmed that, even when the stirring after the quench was conducted at 0 °C for 5 min, **3aa**, **3da**, and **3ea** were obtained in good yields of 97%, 80%, and 87%, respectively, which are comparable with those shown in Table 1 (entry 13) and Fig. 2.

17 In the reactions of **1j** (Fig. 2), **2g** (Fig. 3), and **2h** (Fig. 3), a significant amount of coupling products were obtained as a silyl ether (corresponding to **D** in Fig. 4) and/or an alcohol. Thus, acid treatment was performed to convert the mixture to the target 1,3-dienes, **3ja**, **3ag**, and **3ah**.

18 The stereochemistries of **3ai** and **3ak** were confirmed by NOE spectroscopic experiments.

19 Also when benzaldehyde was employed, neither 1,3-diene nor silyl ether was formed.

20 *trans* β-Methyl stilbenes were often obtained as a byproduct in the functionalizations of allylbenzenes, and not used for the reactions, see the ref. 8 and 11.

21 For comparison with the catalytic amide base generated *in situ*, stoichiometric amounts of NaHMDS and KHMDS were examined in the reaction of **1a** and **2a**, which gave the coupling products, but as mixtures of 1,3-diene **3aa** and alcohol (Scheme S1†). The reagents were also used in the reactions of less reactive substrate **4b** with **2e**, which resulted in the low-yield product formations (Scheme S2†). The results show that the current catalytic amide base system is more effective for the 1,3-diene formation.

22 Similar elimination step was noted in our previous studies, see ref. 14*c*.