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Formal Allylic C(sp³)-H Bond Activation of Alkenes Triggered by a Sodium Amide

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Supporting Information Placeholder

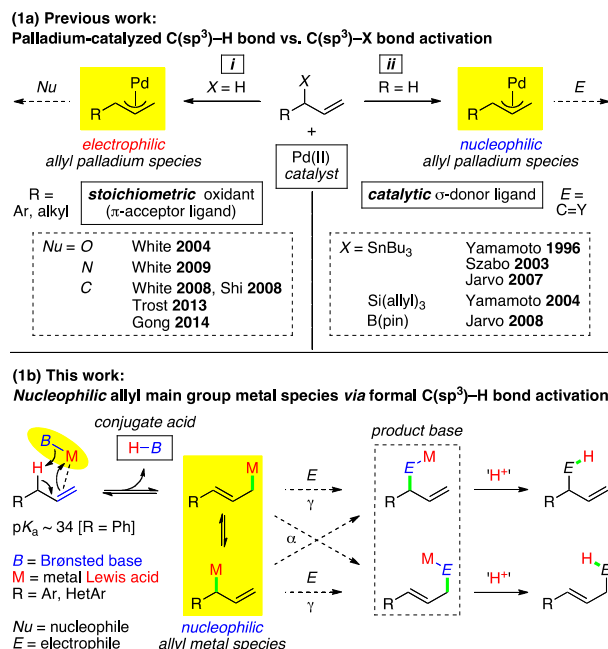
ABSTRACT: The catalytic use of a sodium amide has been exploited for formal allylic C(sp³)-H bond activation of alkenes under mild conditions. Subsequent C-C bond formations with imines have proceeded in high yields with complete regio- and excellent geometric selectivities. Aromatic cyano, chloro, and bromo functionalities have proved to be tolerated by the transition metal-free catalyst. Complex amines bearing a C=C double bond and distinct heteroaromatic units have been prepared in a single step. The critical importance of sodium vs. other s-, p-, d-, and f-block metals as well as metal-free systems has been revealed. In addition, two catalytically active sodium-based intermediates were detected by NMR and HRMS analyses.

The past decades have witnessed tremendous advances in organic chemistry through the development of catalytic C-H bond activation.¹ Typically, transition metal catalysts have been used to activate both C(sp²)-H² and C(sp³)-H³ bonds. In the context of allylic C(sp³)-H bond activation of alkenes, White *et al.* reported in 2004 a ligated palladium(II) acetate catalyst to generate an *electrophilic* allyl-Pd intermediate, which underwent C-O bond formation with a suitable nucleophile Nu (Scheme 1a-i);⁴ this transformation relies on a stoichiometric amount of benzoquinone as an oxidant serving also as a π -acceptor ligand. To date, this *oxidative* C-H bond activation has been exploited for C-N⁵ and C-C⁶ bond formations, respectively, including asymmetric catalysis (Scheme 1a-i). Palladium-free methods include the use of first-row transition metal catalysts in the presence of a stoichiometric oxidant.⁷

Generally, electrophilic allyl-Pd species may undergo *reductive umpolung* to generate a nucleophilic allyl-M intermediate,⁸ but this strategy is precluded for oxidative C-H bond activation. Typically, only metalated or metalloidal allyl substrates were shown to serve as suitable precursors to *nucleophilic* allyl-Pd species (Scheme 1a-ii). In 1996, Yamamoto *et al.* have activated an allyl

stannane to form the corresponding Pd intermediate for nucleophilic addition to a suitable electrophile E.⁹ This methodology relies on the use of an anionic and/or electron-rich σ -donor ligand.¹⁰ Recently, this concept has been extended to the use of silicon¹¹ and boron¹² pro-nucleophiles, respectively (Scheme 1a-ii). In the context of using imine electrophiles,¹³ alternative Pd-free catalysis has been exploited as well.¹⁴ To the best of our knowledge, however, the generation of a *nucleophilic allyl-M* species through *catalytic C-H bond activation* has not been achieved yet.

Scheme 1. Background and concept.



In our program exploiting non-precious metal-base catalysts for formal C-H bond activation, we have become interested in the activation of challenging pro-nucleophiles, such as terminal alkenes, in view of subsequent bond formations (Scheme 1b). Judging from the reported pK_a value of 34 for the allylic hydrogen (R = Ph),¹⁵ we anticipated that a metal π -Lewis acid may be

required to acidify the hydrogen for deprotonation by an amide Brønsted base ($B = \text{NR}_2$). In this scenario, a *nucleophilic* allyl–M species would be generated directly *via* formal C–H bond activation (Scheme 1b). This intermediate may undergo C–C bond formation with a suitable electrophile E (e.g. imine) to form another metal amide (product base), which may account for turnover of the catalytically active allyl–M species. A selective transformation of this type was expected to be challenging because the allyl intermediate may undergo metallotropic rearrangement and γ - or α -selective C–C bond formation thus potentially leading to product mixtures (Scheme 1b). We report here the catalytic use of a sodium amide for formal $\text{C}(\text{sp}^3)$ –H bond activation of alkenes in view of C–C bond formations with imines.

In initial experiments, allyl benzene (**1a**) and benzaldehyde-derived PMP-protected imine **2a** were used as substrates in the presence of a metal amide (10 mol%) at 25 °C (Table 1). The use of commercially available lithium amides in dioxane failed to mediate a C–C bond formation (entries 1–3). When the reaction was carried out in a more Lewis basic solvent, THF, linear adduct **3aa** was obtained in up to 56% yield ($E:Z = >49:1$; entry 1); while regioisomer **3'aa** was not detected, internal alkene **1'a** was observed as a side-product in up to 13% yield ($E:Z = >99:1$; entry 1). When sodium hexamethyldisilazide was used in dioxane, the intended product **3aa** was formed in 98% yield ($E:Z = 99:1$), alongside a trace of **1'a** (entry 4); the yield of **3aa** significantly decreased in THF (entry 4). A screening has revealed that various other etheral solvents and *N*-phenyl-protected imines were compatible with the sodium amide catalyst (see SI). Interestingly, when the stronger potassium base was used the yield of product **3aa** dropped to 23% (entry 5). We also examined a range of other commercially available or easily accessible metal hexamethyldisilazides (entries 6–9). Alkaline earth and p-block metal amides have proved to be unreactive in dioxane or THF (Mg, Ca, Sr, Sn; entry 6). Furthermore, d- and f-block metal amides failed to give **3aa** (Cu, Ag, Zn, Ce, Eu, Gd; entries 7–9). Similarly, the use of alkali metal hydrides –as stronger bases– has proved to be ineffective (entry 10). On the other hand, methyl lithium was shown to trigger a C–C bond formation; product **3aa** and side-product **1'a** were formed in up to 59% and 20% yields, respectively (entry 11). It is noted that the loading of the most effective mediator, $\text{NaN}(\text{SiMe}_3)_2$, was decreased to 5 mol% without loss of activity (entry 12). In this context, the unique ability of sodium and $\text{NaN}(\text{SiMe}_3)_2$ was confirmed through further catalysis control experiments and inductively coupled plasma (ICP) trace element/metal analysis (see SI). In addition, a robustness screening has revealed that several important functionalities were tolerated (see SI). Finally, the critical importance of a metal ion *per se* was demonstrated by using various strong organobases; product **3aa** was *not* obtained under *metal-free* conditions (see SI).

Our study has revealed several remarkable features of this main group metal Brønsted base ‘catalysis’: (1) the connectivity of the alkene and the electronic demand of the imine are clearly distinct from the imino-ene reaction,¹⁶ which relies on transition metal Lewis acid catalysis; (2) the *catalytic* activation of the alkene with a Na amide stands in sharp contrast to the *super-stoichiometric* use of a Li amide for Pd-catalyzed cross-coupling, which also proceeded with opposite regioselectivity;¹⁷ (3) while Na is among the most abundant and cheap metals,¹⁸ only sporadic examples for the catalytic use of a Na amide have been reported in C–C bond formation;¹⁹ (4) the obtained ‘negative’ data (Table 1, entries 6–9) contrast the Brønsted base catalysis with s-, d-, and f-block metal amides in organic synthesis,²⁰ and stress the challenging character of this Na amide-triggered alkene–imine cross-coupling. The fact that Na has proved to be superior to other metals, including Li and K, may be ascribed to favorable values²¹ of electronegativity, formal charge, and ionic radius, all of which should influence both metal Lewis acidity and amide Brønsted basicity.²²

Table 1. Metal–base screening.^a

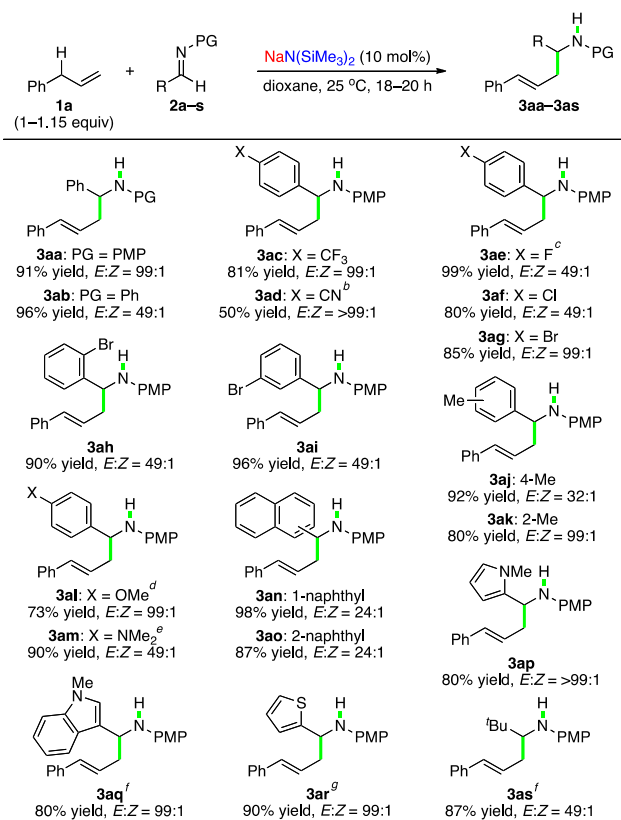
entry	M–base	in dioxane: yield ^a [%]		in THF: yield ^a [%]	
		3aa	1'a	3aa	1'a
1	LiNPr_2	NR	NR	56	13
2	LiTMP	NR	NR	32	2
3	$\text{LiN}(\text{SiMe}_3)_2$	NR	NR	42	4
4 ^{b,c}	$\text{NaN}(\text{SiMe}_3)_2$	98	5	40	0
5	$\text{KN}(\text{SiMe}_3)_2$	23	44	0	37
6	$\text{M}[\text{N}(\text{SiMe}_3)_2]_2$ M = Mg, Ca, Sr, Sn	NR	NR	NR	NR
7	$\text{MN}(\text{SiMe}_3)_2$ M = Cu, Ag	NR	NR	–	–
8	$\text{Zn}[\text{N}(\text{SiMe}_3)_2]_2$	NR	NR	–	–
9	$\text{M}[\text{N}(\text{SiMe}_3)_2]_3$ M = Ce, Eu, Gd	NR	NR	–	–
10	MH M = Li, Na, K [50 mol%]	NR	NR	NR	NR
11 ^d	LiMe	14	2	59	20
12 ^{e,f}	$\text{NaN}(\text{SiMe}_3)_2$ [5 mol%]	99	5	–	–

^a Yields are ¹H NMR yields determined with an aliquot vs. Bn_2O as internal standard. ^b The use of other etheral solvents gave **3aa** in 14–87% yields (see SI). ^c A screening of *N*-protecting groups revealed that *N*-Ph-protected imines are reactive as well (see SI). ^d Nucleophilic methyl addition to the C=N double bond of **2a** was not detected. ^e A robustness screening confirmed that various important functionalities were tolerated by the sodium amide catalyst (see SI). ^f Metal-free strong organobases have proved to be ineffective (see SI).

Next, the imine scope was examined for the Na amide-triggered C–C bond formation using alkene **1a** (Scheme 2). Various electron-poor aromatic imines were successfully converted to cross-coupled products in 50–99% yields ($E:Z = \geq 49:1$; **3ab–ai**). Aromatic rings with *o*-, *m*-, and *p*-substitution and sensitive functional groups –such as cyano, chloro, and bromo– were tolerated by the transition metal-free catalyst. Likewise, the use of electron-rich aromatic imines gave the corresponding products in 73–98% yields ($E:Z = \geq 24:1$; **3aj–ao**). Additionally, a variety of heterocyclic imines were shown to be excellent substrates (80–90% yields, $E:Z = \geq 99:1$; **3ap–**

ar). Moreover, a tertiary aliphatic imine –derived from pivaldehyde– reacted smoothly to give product **3as** in 87% yield (*E:Z* = 49:1).

Scheme 2. Scope of imines.



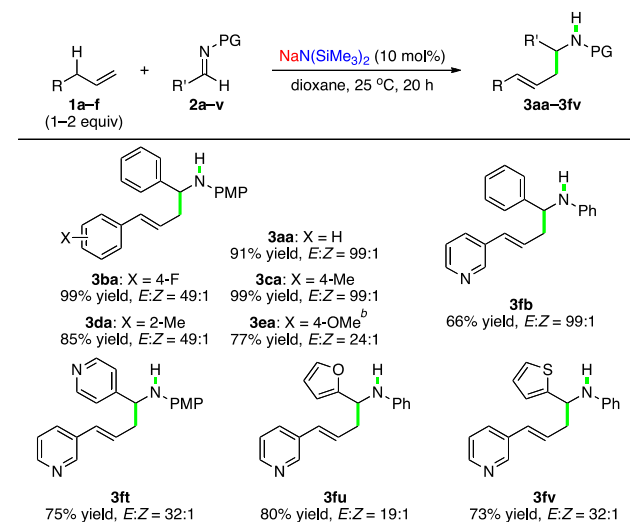
^a All yields are isolated yields after preparative thin-layer chromatography (PTLC). ^b Use of 3 equiv of **1a**. ^c Reaction conducted at 40 °C. ^d Use of 1.8 equiv of **1a** (successive addition). ^e Use of 2.5 equiv of **1a** (successive addition). ^f Use of 2 equiv of **1a** (successive addition). ^g Reaction conducted with 1.5 equiv of **1a** at 60 °C for 72 h.

In addition, the scope of alkenes was examined (Scheme 3). Various substituted allyl benzenes **1b–e** were shown to react smoothly to give the corresponding products in 77–99% yields (*E:Z* = ≥24:1; **3ba–ea**). Furthermore, 3-allyl pyridine (**1f**) has proved to be an excellent pro-nucleophile to give, with a variety of imines, cross-coupled products in 66–80% yields (*E:Z* = ≥19:1). Complex amines bearing a C=C double bond and two electron-poor *N*-heterocycles (**3ft**), or both electron-poor and electron-rich heteroaromatic units (**3fu**, **3fv**), were formed in a single step.

Finally, we investigated the reaction mechanism (Scheme 4). Allyl–Na species **4** was not detectable in the reaction between alkene **1a** and $\text{NaN}(\text{SiMe}_3)_2$ under various conditions (Scheme 4–i); instead, a mixture of isomers **1a** and **1'a** was observed, which may be ascribed to the high reactivity of **4** in the presence of a proton source [HN(SiMe₃)₂]. However, when **1a** was reacted with NaO^tBu/BuLi (1.1 equiv) in THF-*d*₈ at –20 °C, a single resonance at –5.3 ppm was detected in ²³Na NMR spectroscopy, which is consistent with a Na–C species (Scheme 4–ii; see SI).²³ Together with ¹H/¹³C NMR and HRMS data, this intermediate was assigned to be the η^3 -coordinated (*E*)-phenylallyl–Na nucleophile **4** (see SI).

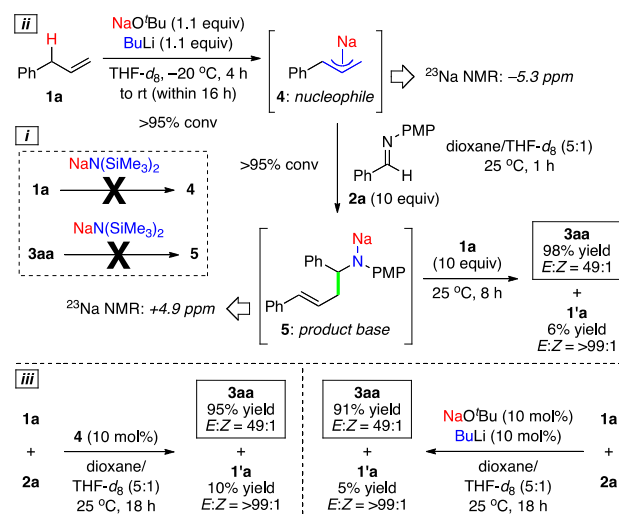
Species **4** underwent C–C bond formation with imine **2a** (10 equiv) to generate the Na–N product base **5** as detected in ²³Na (+4.9 ppm) and ¹H/¹³C NMR spectroscopy (Scheme 4–ii; see SI).²⁴ Species **5** proved to be catalytically active; when **1a** (10 equiv) was added to the mixture, product **3aa** was formed in 98% yield (*E:Z* = 49:1) based on **2a** (Scheme 4–ii). Likewise, species **4** and NaO^tBu/BuLi were shown to catalyze the reaction between **1a** and **2a** to give **3aa** in 95% and 91% yields, respectively (*E:Z* = 49:1; Scheme 4–iii).²⁵ These results are consistent with the data obtained for the catalytic use of $\text{NaN}(\text{SiMe}_3)_2$ (cf. Table 1, entry 4), and suggest that species **4** and **5** are critical intermediates in the developed sodium amide catalysis.

Scheme 3. Scope of alkenes.



^a All yields are isolated yields after preparative thin-layer chromatography (PTLC). ^b Reaction conducted at 40 °C.

Scheme 4. Mechanistic experiments.



In conclusion, we have developed a sodium amide-triggered formal C(sp³)–H bond activation of alkenes under mild conditions, which was exploited for atom-economic C–C bond formations with imines proceeding in high yields with complete regio- and excellent geometric

selectivities. Aromatic cyano, chloro, and bromo functionalities have proved to be tolerated by the transition metal-free catalyst. The critical importance of sodium vs. other s-, p-, d-, and f-block metals as well as metal-free systems has been demonstrated. Two novel catalytically active sodium-based intermediates were detected, which sheds light on the reaction mechanism. This methodology is a rare example for the catalytic use of a sodium amide in C–C bond formation,¹⁹ and should impact the fields of organic synthesis, main group metal chemistry, and earth-abundant¹⁸ metal catalysis.

ASSOCIATED CONTENT

Experimental details and characterization data.

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Notes

[†] These authors contributed equally to this work.

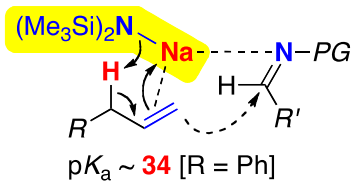
The authors declare no competing financial interest.

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- (23) The direct conversion **1a** → **4** failed when other Na bases (NaNH₂, NaH, NaBu) were used under various conditions.
- (24) The direct conversion **3aa** → **5** failed (Scheme 4–i).
- (25) In contrast, when the Li analogue of **4** was used (10 mol%), product **3aa** was obtained in only 12% yield (*E:Z* = >99:1; see SI).



generation of **nucleophilic allyl-Na** species
via formal catalytic **C(sp³)-H** bond activation

R = Ar, 3-py

R' = Ar, HetAr, ^tBu; PG = PMP, Ph

– transition metal-free method

– 27 examples

– complete regioselectivity

– E:Z = 19:1 ~ >99:1

– detection of novel Na intermediates
