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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 metalfree 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 metalfree 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 $C(sp^2)-H^2$ and $C(sp^3)$ -H³ bonds. In the context of *allylic* $C(sp^3)$ -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-i⁴ 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 metalloid 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.









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 p K_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* ($B = NR_2$). 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 C(sp³)–H bond activation of alkenes in view of C– C bond formations with imines.

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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, NaN(SiMe₃)₂, was decreased to 5 mol% without loss of activity (entry 12). In this context, the unique ability of sodium and NaN(SiMe₃)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 crosscoupling. 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

H Ph 1a (1.1 equiv)	$\begin{array}{c} \begin{array}{c} \text{M-base} \\ (10 \text{ mol\%}) \\ \text{solvent} \\ 25 ^{\circ}\text{C}, 21 \text{ h} \\ \text{N}^{r}\text{PMP} \\ \text{Ph} \\ \text{H} \end{array} \begin{array}{c} \text{E} \\ \text{2a} \\ \text{Ph} \\ \end{array}$	$\begin{array}{c} H \\ Ph \\ \end{pmatrix} \\ N \\ PMP \\ Ph \\ Ph \\ Ph \\ Ph \\ Ph \\ Ph \\ P$	H N-PMP H Ph Ph I'a served E:Z = >99:1 d hylpiperidyl
entry	M-base	in dioxane: yie l d ^a [%] 3aa / 1'a	in THF: yie l d ^a [%] 3aa / 1'a
1	LiN [/] Pr ₂	NR	56 / 13
2	LiTMP	NR	32 / 2
3	LiN(SiMe ₃) ₂	NR	42 / 4
4 ^{b,c}	NaN(SiMe ₃) ₂	98 / 5	40 / 0
5	KN(SiMe ₃) ₂	23 / 44	0 / 37
6	M[N(SiMe ₃) ₂] ₂ M = Mg, Ca, Sr, Sn	NR	NR
7	MN(SiMe ₃) ₂ M = Cu, Ag	NR	-
8	Zn[N(SiMe ₃) ₂] ₂	NR	-
9	M[N(SiMe ₃) ₂] ₃ M = Ce, Eu, Gd	NR	-
10	MH M = Li, Na, K [50 mol%]	NR	NR
11 ^d	LiMe	14 / 2	59 / 20
12 ^{<i>e,f</i>}	NaN(SiMe ₃) ₂ [5 mol%]	99 / 5	-

^a Yields are ¹H NMR yields determined with an aliquot vs. Bn₂O as internal standard. ^b The use of other etheral solvents gave **3aa** in 14–87% yields (see SI). ^c A screening of Av-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 ($E:Z = \ge 49:1$; **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 ($E:Z = \ge 24:1$; **3aj–ao**). Additionally, a variety of heterocyclic imines were shown to be excellent substrates (80–90% yields, $E:Z = \ge 99:1$; **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 ^oC. ^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 ^oC for 72 h.

In addition, the scope of alkenes was examined (Scheme 3). Variously substituted allyl benzenes **1b–e** were shown to react smoothly to give the corresponding products in 77–99% yields ($E:Z = \ge 24:1$; **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 ($E:Z = \ge 19:1$). 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 NaN(SiMe₃)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'Bu/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'Bu/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 NaN(SiMe₃)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 $^o{\rm C}.$

Scheme 4. Mechanistic experiments.



In conclusion, we have developed a sodium amide-triggered formal $C(sp^3)$ –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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(24) The direct conversion **3aa** \rightarrow **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).

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Scheme 1. Background and concept.

(1a) Previous work:



(1b) This work:

Nucleophilic allyl main group metal species via formal C(sp³)-H bond activation



Table 1. Metal–base screening. ^ª						
	H Ph 1a (1.1 equiv)	$ \begin{array}{c} M-base \\ (10 mol\%) \\ \hline solvent \\ 25 ^{\circ}C, 21 h \\ \hline Ph H \\ \end{array} $ $ \begin{array}{c} Ph \\ E:2 \\ Ph \\ H \end{array} $	H H H $h \rightarrow N$ PMP + Ph H 3aa $3'aZ = >49:1$ not obs PMP = 4-methoxypheny TMP = 2,2,6,6-tetrameth	PMP H Ph H Ph H Ph H Ph H Ph H E:Z = >99:1		
-	entry	M-base	in dioxane: yield ^a [%] 3aa / 1'a	in THF: yield ^a [%] 3aa / 1'a		
	1	LiN ⁱ Pr ₂	NR	56 / 13		
	2	LiTMP	NR	32 / 2		
	3	LiN(SiMe ₃) ₂	NR	42 / 4		
	4 ^{<i>b</i>,<i>c</i>}	NaN(SiMe ₃) ₂	98 / 5	40 / 0		
	5	KN(SiMe ₃) ₂	23 / 44	0 / 37		
	6	M[N(SiMe ₃) ₂] ₂ M = Mg, Ca, Sr, Sn	NR	NR		
	7	MN(SiMe ₃) ₂ M = Cu, Ag	NR	_		
	8	Zn[N(SiMe ₃) ₂] ₂	NR	-		
	9	M[N(SiMe ₃) ₂] ₃ M = Ce, Eu, Gd	NR	_		
	10	MH M = Li, Na, K [50 mol%]	NR	NR		
	11 ^{<i>d</i>}	LiMe	14 / 2	59 / 20		
	12 ^{<i>e</i>,<i>f</i>}	NaN(SiMe ₃) ₂ [5 mol%]	99 / 5	_		

^a Yields are ¹H NMR yields determined with an aliquot vs. Bn₂O 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).



^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.



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



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4	(Me ₃ Si) ₂ N	concretion of much ambility alloy No maning	
5		generation of nucleophilic allyi–Na species	
6		via formal <mark>catalytic</mark> C(sp ³)–H bond activation	
7	R R'	transition motal frag mathed	
8	nK = 24 [P - Ph]	- Italisiilon metal-nee <mark>methou</mark> 27 oxomplos	
9	$pr_a \sim 34 [n = rij]$	- 27 examples	
3	B = Ar 3 - pv	$= \frac{1}{10} - \frac{10}{10} = 1$	
10	B' = Ar HetAr ^t Bu: $PG = PMP$	$= 2.2 = 10.1 \approx 200.1$	
11	H = AI, HetAI, Du, H = HWI		
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