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1,3,2-Diazaphospholenes Catalyze the Conjugate Reduction of Substituted Acrylic Acids

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Abstract: The potent nucleophilicity and remarkably low basicity of 1,3,2-diazaphospholenes (DAPs) is exploited in a catalytic, metal-free 1,4-reduction of free α,β-unsaturated carboxylic acids. Notably, the reduction occurs without a prior deprotonation of the carboxylic acid moiety and hence does not consume an additional hydride equivalent. This highlights the excellent nucleophilic character and low basicity of DAP-hydrides. Functional groups such as Cbz group or alkyl halides which can be problematic with classical transition-metal catalysts are well tolerated in the DAP-catalyzed process. Moreover, the transformation is characterized by a low catalyst loading, mild reaction conditions at ambient temperature as well as fast reaction times and high yields. The proof-of-principle for a catalytic enantioselective version is described.

Reduction reactions constitute some of the most industrially and academically important organic transformations.[1] For instance, the selective conjugate reduction of widely distributed α,β-unsaturated carbonyl compounds provides an economical means to access value-added chemicals from readily available substrates.[2] Numerous catalytic systems have been established to facilitate such transformations.[3] These methodologies commonly rely on the combination of a transition-metal catalyst and a stoichiometric reductant such as H_2.[4,5] In order to circumvent the costs, environmental impact and purification issues that may be associated with the use of rare transition-metals, the search for efficient metal-free catalyst systems has garnered growing interest.[6] Among a wide variety of metal-free approaches,[7] including frustrated Lewis pairs (FLPs),[8] and Hantzsch esters with amine catalysts[9] have emerged. In this context, the ability of 1,3,2-diazaphospholenes (DAPs)[10] to catalyze the reduction of functional groups such as aldehydes and ketones,[11a] imines,[11b] pyridines,[11c,d] azobenzenes,[11e] and CO_2,[11f] has been recently discovered (Figure 1). Moreover, DAPs display a profound selectivity for the 1,4-reduction of α,β-unsaturated carbonyl compounds.[12,13] Further advances have been made by developing chiral DAPs capable of stereoselectively reducing prochiral substrates.[14] This reactivity results from the Umpolung of the P–H bond of DAPs, which in turn is a consequence of the partial delocalization of the 6π electrons of the 5-membered ring.[15] Increased electron density in the σ*-orbital of P–H bond simultaneously weakens the bond and induces a reversal of the typical bond polarity. Cheng and co-workers reported that the prototypical DAP (**P1**) is the most nucleophilic hydride donor ever quantified on the Mayr nucleophilicity scale.[16] We hypothesized that this remarkable property should be leveraged to facilitate more challenging hydride additions.

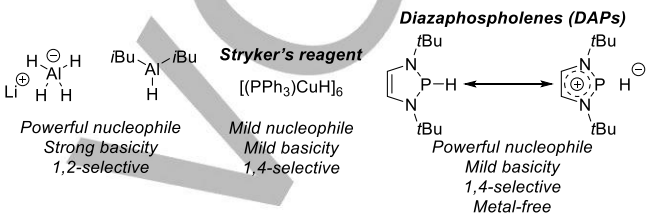
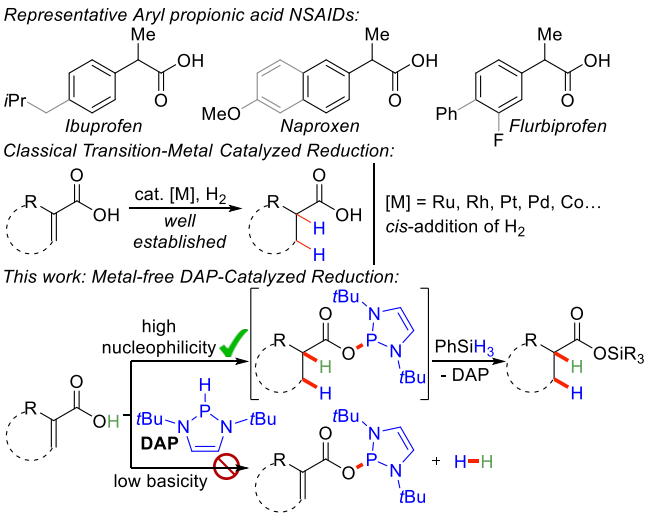


Figure 1. 1,3,2-Diazaphospholenes exhibit Umpolung reactivity of the P–H bond leading to molecular hydrides that are competent reducing agents.

Non-steroidal anti-inflammatory drugs (NSAIDs) of the aryl propionic acid class such as ibuprofen, naproxen or flurbiprofen[17] are important drugs and could be accessed by a conjugate reduction of corresponding substituted acrylic acids (Scheme 1). Generally, a variety of homo- and heterogeneous transition-metal catalyzed processes are reported for the direct hydrogenation of substituted acrylic acids.[18-20] However, the inherent acidic nature of a carboxylic acid presents a challenge for the development of hydridic, metal-free alternatives. Of further note is the propensity for carboxylic acids to undergo reduction at the carbonyl carbon.[21] Therefore, a catalyst carrying a hydride with excellent nucleophilicity and low basicity, capable of selectively delivering the hydride faster than it deprotonates the acid, is desirable. Herein, we report the direct conjugate reduction of α,β-unsaturated carboxylic acids using a DAP-catalyst and phenylsilane as the stoichiometric reductant.



Scheme 1. Aryl propionic acid NSAIDs are a biologically important class of compounds; DAP-catalyzed metal-free conjugate reduction strategy.

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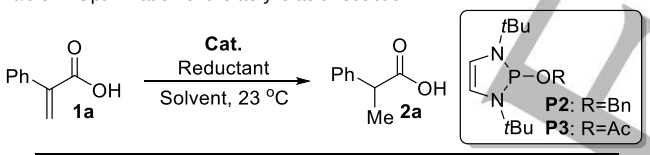
We commenced our investigations by studying the reduction of 2-phenylacrylic acid (**1a**). The combination of DAP precatalyst **P2** and pinacol borane as the terminal reductant in THF cleanly provided 2-phenylpropionic acid (**2a**), in 93 % yield after just 10 minutes (Table 1, entry 1). We next examined whether other convenient hydride sources such as silanes could also serve as the terminal reductants. No conversion was observed when using with Ph_2SiH_2 in combination with **P2** (entry 2). However, switching to pre-catalyst **P3**, bearing an acetate group instead of the benzyloxy substituent on the phosphorous atom, complete conversion of **1a** was observed, furnishing **2a** in 85 % yield (entry 3). Interestingly, while both Ph_2SiH_2 and $PhSiH_3$ (87 %, entry 4) delivered the desired product in excellent yields, no other silane, including related Ph_3SiH, gave any conversion at all (see SI for full optimization). For both Ph_2SiH_2 and $PhSiH_3$, all available hydrides of the silane were able to induce catalyst turnover (0.35 eq. $PhSiH_3$ corresponding to 1.05 hydride equivalents) (entry 5). Selecting $PhSiH_3$ as the reducing agent of choice, we examined the effects of different solvents on the reaction outcome (entries 6-8). Complete consumption of starting material **1a** occurred in toluene or acetonitrile, although a significant decrease in yield of **2a** was observed in the latter. Conversely, using Et_2O caused a dramatic decrease in the rate of catalyst turnover, with only 64 % conversion observed, giving **2a** in low yield (37 %). In contrast, the catalyst loading could be reduced to 2 mol % in THF and full conversion was maintained after 2 hours (97 % yield of, entry 9). A control experiment with no catalyst resulted in complete recovery of **1a** (entry 10). When run on a gram scale (10 mmol substrate **1a**), the catalyst loading could be reduced to 0.5 mol% (entry 11). The transformation maintained its excellent efficiency, giving product **2a** in quantitative isolated yield without the need for temperature control (no heating or cryogenic conditions).

Table 1. Optimization of the acrylic acid reduction.

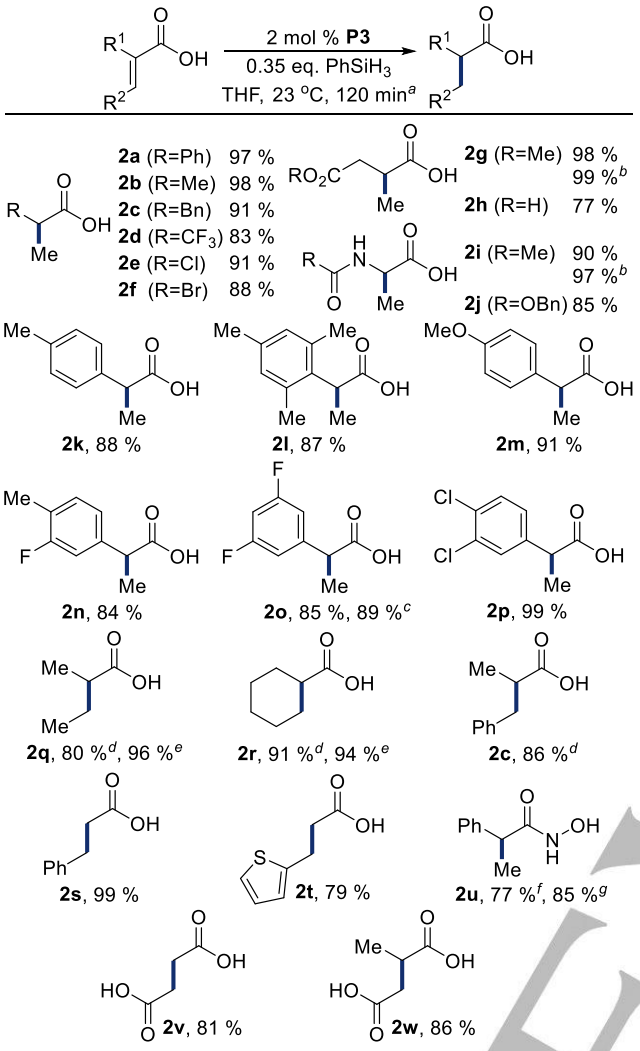


Entry	**Cat.** (mol %)	Reductant (eq.)	Solvent	t (min)	% Yield
1[a]	**P2** (10)	PinBH (1.1)	THF	10	93
2[a]	**P2** (10)	Ph_2SiH_2 (1.1)	THF	10	0
3[a]	**P3** (10)	Ph_2SiH_2 (1.1)	THF	10	85
4[a]	**P3** (10)	$PhSiH_3$ (1.1)	THF	10	87
5[a]	**P3** (10)	$PhSiH_3$ (0.35)	THF	10	92
6[a]	**P3** (10)	$PhSiH_3$ (0.35)	PhMe	10	88
7[a]	**P3** (10)	$PhSiH_3$ (0.35)	MeCN	10	67
8[a]	**P2** (10)	$PhSiH_3$ (0.35)	Et_2O	10	37
9[a]	**P3** (2)	$PhSiH_3$ (0.35)	THF	120	97
10[a]	-	$PhSiH_3$ (0.35)	THF	360	0
11[b]	**P3** (0.5)	$PhSiH_3$ (0.35)	THF	360	>99

[a] 14.82 mg (0.1 mmol) of **1a** with the specified amount of reductant and catalyst in 100 µL of the specified solvent (1.00 M) for the indicated time at 23 °C; [b] 1.482 g (10 mmol) of **1a**, 432 µL (3.50 mmol) $PhSiH_3$, 12.9 mg (0.05 mmol) **P3**, in 10 mL THF for 6 h at 23 °C.

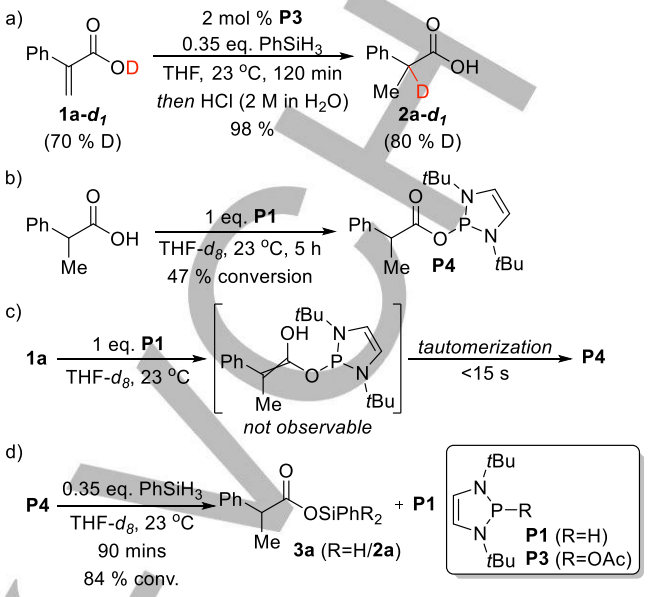
Using the optimized reaction conditions, the scope of the reaction was investigated. A wide variety of functionality was tolerated at both the C-2 and C-3 positions of acrylic acids **1**, leading to propionic acids **2a**-**2u** (Scheme 2). Products **2b** and **2c**, bearing alkyl substitution at the C-2 position were accessed in excellent yields. Trifluoromethylated derivative **2d** was also well tolerated in the reaction. Halo-substituted substrates **1e** and **1f** were converted in excellent yields to corresponding saturated α-halo acids **2e** and **2f**. Notably, no observable traces of elimination or reduction of the C–X bond was detected. Ester groups were equally well tolerated, permitting for instance access to **2g** in 98 % yield. A second free carboxylic acid on the substrate proved to be neither a hindrance to the reaction nor consumed a hydride equivalent, giving product **2h** in 77 % isolated yield. Electronically modified acrylic acids, such as protected dehydroalanine substrates **1i** and **1j**, were efficiently engaged in the reaction, giving the mono-protected amino acids, **2i** and **2j**, in excellent yields of 90 % and 85 % respectively. Of further note is the chemoselectivity observed in the case of substrate **2j**. Under metal-catalyzed hydrogenation conditions, the benzyloxy-moiety of the Cbz protecting group would likely undergo hydrogenolysis leading to undesirable deprotection of the amino group. Under the present DAP catalysis, no such side-reactivity occurs. Acrylic acids bearing a variety of different aryl-substituents at the C-2 position were prepared, and in all cases, these were efficiently reduced to the corresponding 2-arylpropionic acids (**2k**-**2p**). Increased steric hindrance around the double bond was well tolerated, giving **2l** in 87 % yield. The more electron-rich 2-(4-methoxyphenyl)acrylic acid was smoothly reduced to **2m** in excellent yield. Substrates bearing aryl fluorides could be used, giving products **2n** and **2o** in excellent yields, while 2-(3,4-dichlorophenyl)acrylic acid was equally adept in the reaction, enabling the isolation of **2p** in virtually quantitative yield. Examples **2o** and **2p** demonstrate that electron poor aryl groups are tolerated, further highlighting the generality of this method. We then examined the suitability of a range of 2,3-disubstituted substrates. While still viable, we observed a decrease in their rate of reduction, for which we could compensate with an extra equivalent of hydride. Under these conditions, products **2q** and **2r** were cleanly obtained after 6 hours. Additionally, under the modified conditions, product **2c** was obtained from (*E*)-2-methyl-3-phenylacrylic acid in 86 % yield. The use of C-3 substituted substrates (lacking the additional substitution at C-2) do not require neither any extra hydride equivalents nor prolonged reaction times. Instead, **2s** and **2t** were obtained in yields of 99 % and 79 % respectively after 2 hours with 0.35 equivalents of $PhSiH_3$ (1.05 equivalent total hydride). Moreover, we also demonstrated that this methodology can be used for the reduction of other acidic substrates such as α,β-unsaturated hydroxamic acid **1u**. Notably, in this case, no catalyst turnover occurred from the reduced hydroxamate. However, the addition of 2 mol % *N*-methylimidazole as a co-catalyst promoted the necessary σ-bond metathesis, enabling the formation of **2u** in 77 % isolated yield. We believe that this additive is able to coordinate to the phosphorus atom of the catalyst, thereby weakening the bond between the DAP and the hydroxamate. Consequently, the σ-bond metathesis with the silane is accelerated. The conjugated diacids, fumaric acid and mesaconic acid, were efficiently reduced to their saturated congeners, **2v** and **2w**, in respective yields of 81 % and 86 %. In order to further prove the general applicability and synthetic utility of the methodology, selected substrates (**1g**, **1i**, **1o**, **1q**, **1r** and **1u**) were reduced on a increased scale (either 5 or 10 mmol of substrate). Pleasingly, for these larger scale reactions, the catalyst loading could be further reduced to 0.05 mol% and full conversion was still observed. Moreover, on each case, the isolated yield of the product on these

larger scales was found to be superior to the yield of the exploratory 0.2 mmol scale.



Scheme 2. Scope of the DAP-catalyzed acrylic acid reduction. [a] 0.2 mmol substrate, 8.63 µL (0.07 mmol) $PhSiH_3$, 1.03 mg (4 µmol) **P3** in 0.2 mL THF for 2 h at 23 °C; [b] 10 mmol substrate, 432 µL (3.50 mmol) $PhSiH_3$, 12.9 mg (0.05 mmol) **P3**, in 10 mL THF for 6 h at 23 °C; [c] 5 mmol substrate, 216 µL (1.75 mmol) $PhSiH_3$, 6.5 mg (25 µmol) **P3**, in 5 mL THF for 6 h at 23 °C; [d] 0.2 mmol substrate, 17.3 µL (0.14 mmol) $PhSiH_3$, 1.03 mg (4.00 µmol) **P3** in 0.2 mL THF for 6 h at 23 °C; [e] 10 mmol substrate, 863 µL (7 mmol) $PhSiH_3$, 12.9 mg (0.05 mmol) **P3**, in 10 mL THF for 6 h at 23 °C; [f] 0.2 mmol substrate, 8.63 µL (0.07 mmol) $PhSiH_3$, 1.03 mg (4.00 µmol) **P3**, 0.3 µL (4 µmol) 1-methylimidazole in 0.2 mL THF for 2 h at 23 °C; [g] 5.0 mmol substrate, 216 µL (1.75 mmol) $PhSiH_3$, 6.5 mg (25.0 µmol) **P3**, 2 µL (0.025 mmol) 1-methylimidazole in 5 mL THF for 2 h at 23 °C.

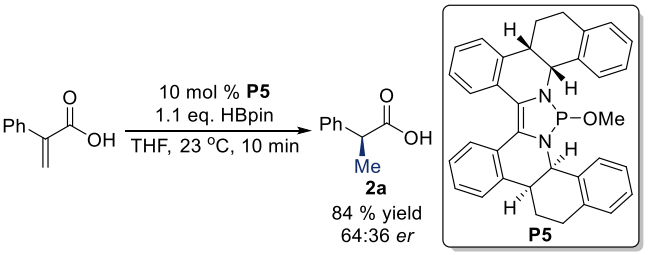
To better understand the transformation, a series of experiments were conducted to elucidate the underlying processes (Scheme 3). Deuterated acrylic acid **1a-*d*$_1$** (70 % D) was subjected to the standard reaction conditions (a). Analysis of the formed product revealed selective deuterium incorporation at the α-position of the acid occurred (80 % D). This indicates that the carboxylic acid proton tautomerises prior to the work-up reaction quench. The reaction between preformed DAP-hydride (**P1**) and saturated carboxylic acid **2a** confirmed the low basicity of the DAPs (b). Deprotonation of acid **2a** by stoichiometric amounts of **P1** occurred *very slowly* at ambient temperature and less than 50 % conversion to **P4** was observed after 5 h (see SI for details). To compare this value to the relative rates of the reduction process, **1a** was reacted with one equivalent of **P1** (c). Both the reduction and tautomerization of intermediate **Int-I** occurred *virtually instantaneously* cleanly giving **P4** as the only observable product. Upon addition of $PhSiH_3$ to the reaction reaction mixture, a slow conversion of **P4** to **3a** with concomitant regeneration of **P1** was observed, indicating this to be the rate-limiting step of the catalytic cycle (d).



Scheme 3. Mechanistic studies of the DAP-catalyzed acrylic acid reduction: a) deuterium labelling shows that proton transfer occurs prior to aqueous quenching of the reaction, the erroneously low value for deuterium incorporation of substrate **1a-*d1*** is most likely because of exchange between the labile deuterium with trace water; b) quenching of the DAP-hydride with an acidic proton occurs very slowly; c) reduction of the substrate and subsequent tautomerization occurs rapidly; d) stoichiometric experiments indicate the rate limiting step of the catalytic cycle is the σ-bond metathesis.

Consequently, the tautomerization process takes place while the DAP is still covalently bound to the intermediate and in close proximity. This implies that a suitable chiral DAP catalyst might be able to induce an enantioselective tautomerization, leading to enantio-enriched propionic acid derivatives. To verify this hypothesis, chiral DAP pre-catalyst **P5**[13b] was employed in the reduction of **1a** with pinacol borane (Scheme 4). Pleasingly, this reaction led to the formation of **2a** in 84 % yield with an enantiomeric ratio of 64:36 as determined by chiral HPLC analysis. This result is a first proof-of-principle that chiral DAPs can catalyze an enantioselective reduction of substituted acrylic acids.

Scheme 4. Catalytic reduction of **1a** followed by enantioselective proton-transfer.



In conclusion, we have developed a 1,3,2-diazaphospholene catalyzed 1,4-reduction of free acrylic acids. This reaction occurs under mild conditions and exhibits excellent functional group tolerance. The low catalyst loading, fast reaction times and the use of $PhSiH_3$ as convenient terminal reductant are salient

features of this transformation. The methodology is particularly attractive as it showcases the unique properties of the 1,3,2-diazaphospholenes whereby they are very potent nucleophiles, yet displaying remarkably low basicity. As such, the reaction proceeds *without* quenching by the acidic proton of the carboxylic acid. The process can be rendered enantioselective. We will dedicate future efforts towards developing new chiral diazaphospholene catalysts capable of achieving improved levels of enantioinduction.

Keywords: diazaphospholene • reduction • catalysis • molecular hydride • nucleophilic

[1] a) *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2006**; b) *Modern Reduction Methods* (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**; c) D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621; d) *Homogeneous Hydrogenation with Non-Precious Catalysts* (Ed.: J. F. Teichert) Wiley-VCH, Weinheim, **2019**.

[2] X. Tan, H. Lv, X. Zhang in *Science of Synthesis: Catalytic Reduction in Organic Synthesis 1* (Ed.: J. G. de Vries), Thieme, Stuttgart, p 7.

[3] S. Rendler, M. Oestreich, *Angew. Chem. Int Ed.* **2007**, *46*, 498-504 b) C. Deutsch, N, Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916-2927; c) A. V. Malkov, K. Lawson, *Top. Organomet. Chem.* **2016**, *58*, 207-220.

[4] a) P. Cheruku, A. Paptchikhine, T. L. Church, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8285-8289; b) D. Rageot, D. Woodmansee, B. Pugin, A. Pfaltz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9598-9601; c) S. Kraft, K. Ryan, R. B. Kargbo, *J. Am. Chem. Soc.* **2017**, *139*, 11630-11641; d) J. Muzart, *Eur. J. Org. Chem.* **2015**, 5693-5707; e) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497-511.

[5] For examples using non-precious transition metals, see: a) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818-8823; b) S. Z. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794-13807; c) R. J. Trovitch, E. Lobkovsky, E. Bill, P. J. Chirik, *Organometallics*, **2008**, *27*, 1470-1478; d) M. R. Friedfeld, M. Shevlin, J. M. Hoyt, S. W. Krska, M. T. Tudge, P. J. Chirik, *Science*, **2013**, *342*, 1076-1080; e) R. P. Yu, J. M. Darmon, C. Milsmann, G. W. Margulieux, S. C. E. Stieber, S. DeBeer, P. J. Chirik, *J. Am. Chem. Soc.* **2013**, *135*, 13168-13184; f) P. J. Chirik, *Acc. Chem. Res.* **2015**, *48*, 1687-1695; g) G. A. Filonenko, R. van Putten, E. J. M. Hensen, E. A. Pidko, *Chem. Soc. Rev.* **2018**, *47*, 1459-1483; h) B. M. Zimmerman, S. C. K. Kobosil, J. F. Teichert, *Chem. Commun.* **2019**, *55*, 2293-2296.

[6] a) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084-1105; b) K. L. Hodge, J. E. Goldberger, *J. Am. Chem. Soc.* **2019**, *141*, 19969-19972; c) L. Longwitz, T. Werner, *Angew. Chem. Int. Ed.* **2020**, *59*, 2760-2763; d) Y. Nishiyama, Y. Makino, S. Hamanaka, A. Ogawa, N. Sonoda, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1682-1684; e) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem. Int. Ed.* **2004**, *43*, 6660-6662; f) M. Sugiura, Y. Ashikari, Y. Takahashi, K. Yamaguchi, S. Kotani, M. Nakajima, *J. Org. Chem.* **2019**, *84*, 11458-11473; g) X. Xia, Z. Lau, P. H. Toy, *Synlett*, **2019**, *30*, 1100-1104.

[7] *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.

[8] a) L. J. Hounjet, D. W. Stephan, *Org. Process. Res. Dev.* **2014**, *18*, 386-391; b) D. J. Scott, M. J. Fuchter, A. E. Ashley, *Chem. Soc. Rev.* **2017**, *46*, 5689-5700; c) J. Paradies, *Top. Organomet. Chem.* **2018**, *62*, 193-216.

[9] C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498-2518.

[10] a) D. Gudat, A. Haghverdi, M. Nieger, *Angew. Chem. Int. Ed.* **2000**, *39*, 3084-3086; b) D. Gudat, *Dalton Trans.* **2016**, *45*, 5896-5907; c) T. Lundrigan, C.-H. Tien, K. N. Robertson, A. W. H. Speed, *Chem. Commun.* **2020**, DOI: 10.1039/D0CC01072C.

[11] a) C. C. Chong, H. Hirao, R. Kinjo, *Angew. Chem. Int. Ed.* **2015**, *54*, 190-194; b) M. R. Adams, C. H. Tien, B. S. N. Huchenski, M. J. Ferguson, A. W. H. Speed, *Angew. Chem. Int. Ed.* **2017**, *56*, 6268-6271; c) B. Rao, C. C. Chong, R. Kinjo, *J. Am. Chem. Soc.* **2018**, *140*, 652-656; d) T. Hynes, E. N. Welsh, R. McDonald, M. J. Ferguson, A. W. H. Speed, *Organometallics* **2018**, *37*, 841-844; e) C. C. Chong, H. Hirao, R. Kinjo, *Angew. Chem. Int. Ed.* **2014**, *53*, 3342-3346; f) C. C. Chong, R. Kinjo, *Angew. Chem. Int. Ed.* **2015**, *54*, 12116-12120.

[12] S. Burck, D. Gudat, M. Nieger, W.-W. Du Mont, *J. Am. Chem. Soc.* **2006**, *128*, 3946-3955.

[13] a) C. C. Chong, B. Rao, R. Kinjo, *ACS Catal.* **2017**, *7*, 5814-5819; b) J. H. Reed, P. A. Donets, S. Miaskiewicz, N. Cramer, *Angew. Chem. Int. Ed.* **2019**, *58*, 8893-8897.

[14] a) M. R. Adams, C. H. Tien, R. McDonald, A. W. H. Speed, *Angew. Chem. Int. Ed.* **2017**, *56*, 16660-16663; b) S. Miaskiewicz, J. H. Reed, P. A. Donets, C. C. Oliveira, N. Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 4039-4042; c) T. Lundrigan, E. N. Welsh, T. Hynes, C.-H. Tien, M. R. Adams, K. R. Roy, K. N. Robertson, A. W. H. Speed, *J. Am. Chem. Soc.* **2019**, *141*, 14083-14088.

[15] D. Gudat, A. Haghverdi, W. Hoffbauer, *Magn. Reson. Chem.* **2002**, *40*, 589-594.

[16] J. Zhang, J.-D. Yang, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2019**, *58*, 5983-5987.

[17] a) T. Y. Shen, *Angew. Chem. Int. Ed.* **1972**, *11*, 460-472; b) D. Lednicer, L. A. Mitscher in *The Organic Chemistry of Drug Synthesis Vol. 3*, Wiley, New York, **1984**.

[18] For a review, see: S. Khumsubdee, K. Burgess, *ACS Catal.* **2013**, *3*, 237-249.

[19] For selected examples using Rh, Ir, or Ru catalysts, see: a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567-2568; b) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174-3176; c) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007; d) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022; e) M. J. Burk, P. D. de Koning, T. M. Grote, M. S. Hoekstra, G. Hoge, R. A. Jennings, W. S. Kissel, T. V. Le, I. C. Lennon, T. A. Mulhern, J. A. Ramsden, R. A. Wade, *J. Org. Chem.* **2003**, *68*, 5731-5734; f) D. M. Tellers, J. C. McWilliams, G. Humphrey, M. Journet, L. DiMichele, J. Hinksmon, A. E. McKeown, T. Rosner, Y. Sun, R. D. Tillyer, *J. Am. Chem. Soc.* **2006**, *128*, 17063-17073; g) S. Li; S.-F. Zhu, C.-M. Zhang, S. Song, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 8584-8585; h) S. Karlsson, H. Sörenson, S. M. Andersen, A. Cruz, P. Ryberg, *Org. Process Res. Dev.* **2016**, *20*, 262-269; i) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2017**, *50*, 988-1001.

[20] For the use of non-precious transition metal catalysts, see: H. Zhong, M. Shevlin, P. J. Chirik, *J. Am. Chem. Soc.* DOI: 10.1021/jacs.9b13876.

[21] a) Y. Zhou, J. S. Bandar, R. Y. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2018**, *140*, 606-609; b) D. Bézier, S. Park, M. Brookhart, *Org. Lett.* **2013**, *15*, 496-499.

10.1002/cctc.202000662

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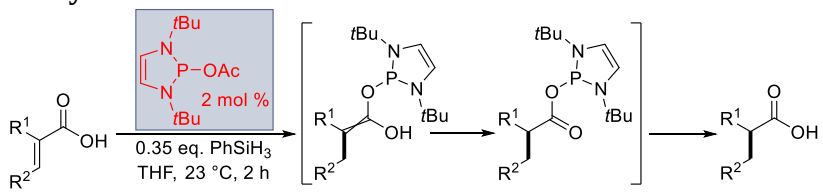

A 1,3,2-diazaphospholene (DAP) catalyst in conjunction with $PhSiH_3$ enables the direct conjugate reduction of substituted α,β-unsaturated carboxylic acids without prior deprotonation, highlighting its remarkably potent nucleophilicity and yet low basicity. The transformation is characterized by a low catalyst loading, mild reaction conditions at ambient temperature as well as fast reaction times and tolerates functional groups such as Cbz group or alkyl halides that can be problematic with classical reduction catalysts.