Organic Synthesis

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Pd-Catalyzed Cleavage of Benzylic Nitro Bonds: New Opportunities for Asymmetric Synthesis**

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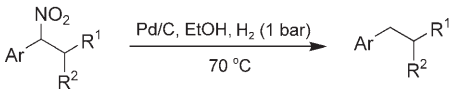
The chemistry of the nitro group finds itself in the midst of a renaissance in the context of asymmetric catalysis.[1] The fact that nitronates can be generated under mild conditions has led to a number of C–C bond-forming reactions. The electrophilic character of nitroalkenes renders them versatile acceptors in a variety of conjugate addition reactions. However, the nitro group is not commonly encountered in natural products or pharmacologically relevant structures. Thus, in fostering the use of organonitro compounds, it is important to develop the synthetic chemistry of this functional group. Herein, we note that exposure of benzylic nitroalkanes to Pd/C/H_2 leads to heterolytic C–N bond reduction in good yields to give the parent alkanes [Eq. (1)]. This reaction is noteworthy as it



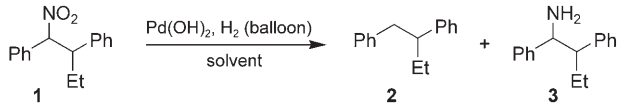
(1)

significantly expands the scope of building blocks that can be accessed through the application of modern methods involving organonitro compounds. Additionally, we document some interesting mechanistic aspects of the reaction.

The need for processes that transform the nitro group into more common functionalities has long been appreciated. These include their conversion into oximes, *N*-hydroxyamines, amines, carboxylic acids, aldehydes, ketones, and nitriles.[2] Less common is the reductive cleavage of organonitro compounds to the corresponding alkanes.[3] In general, these methods suffer from the use of unsavoury reagents (for example, MeSNa, NaTeH, nBu$_3$SnH, or $SnCl_4$) in stoichiometric quantities and from limitations in their scope. Conditions have been reported which involve the use of 10 mol% n-Bu$_3$SnH and $PhSiH_3$ (0.5 equiv), however, the substrates reported contain tertiary nitroalkanes, with 2-nitromalonate as the sole exception.[4] On exposure of benzylic (or allylic) and tertiary nitroalkanes to Pd/H_2, the *N*-benzylamines have been the desired end products, and C–NO_2 bond cleavage, when observed, deemed an undesirable side reaction.[5,6] We decided to investigate the heterolytic reductive cleavage of secondary benzylic organonitro compounds (ArCH(NO_2)R→ArCH_2R). The use of the rich chemistry of the nitro functionality in combination with the subsequent implementation of such a reductive cleavage would allow access to products otherwise difficult to prepare.[7] Importantly, although more difficult and without precedent, the reductive heterolytic cleavage of secondary benzylic nitro groups would effectively lead to removal of the nitro group without the concomitant generation of a stereogenic center.

In initial investigations we observed that treatment of test substrate **1** with H_2 (balloon) at 23 °C or 0 °C in the presence of Pd(OH)$_2$ (50% water/weight) in MeOH or EtOH afforded mixtures of alkane **2** along with amine **3** (Table 1, entries 1 and 2). This was surprising because evidence from previous studies suggested that reduction of the nitro group to the corresponding amine would dominate.[8] Further investigations revealed that the formation of the amine was completely suppressed at 60 °C (Table 1, entries 3 and 4). We next examined the effect of other solvents. The use of ethyl acetate afforded a mixture consisting of **1**, cleavage product, and traces of amine **3** (Table 1, entry 5). With other solvents, such as THF, DMF, or toluene, full conversion into **2** was observed (Table 1, entries 6–8).

Table 1: Study into the effects of solvent and temperature.



	Solv. (T [°C])	Prod. (ratio)		Solv. (T [°C])	Prod.
1	MeOH (23)	**2**:**3** (3:2)	**5**	EtOAc (60)	**1**, **2**, and **3**
2	EtOH (0)	**2**:**3** (1/1)	**6**	THF (60)	**2**
3	MeOH (60)	**2**	**7**	DMF[a] (90)	**2**
4	EtOH (70)	**2**	**8**	toluene (85)	**2**

[a] DMF = dimethylformamide.

We then investigated the effect of the catalyst. Several sources of Pd(OH)$_2$ and Pd/C were used, giving similar conversion and yield. The use of a homogenous catalyst, such as [Pd(Ph$_3$P)$_4$], led to no reaction. The use of Pt/C gave only 18% conversion into amine **3**, with none of cleavage product **2**. Rh/charcoal gave selectively 89% for amine **3** and no cleavage product.

A range of secondary benzylic nitro compounds was synthesized and subjected to the optimized conditions for reductive heterolysis (Table 2). In all cases, treatment of the

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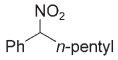
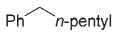
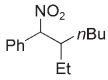
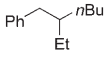
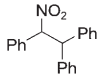
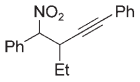
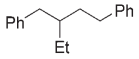
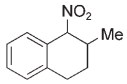
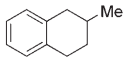
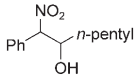
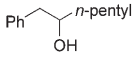
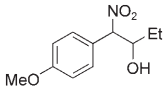
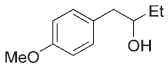
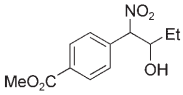
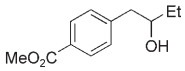
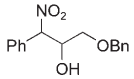
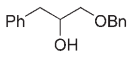
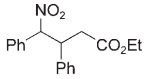
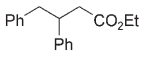
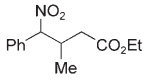
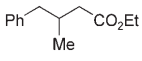
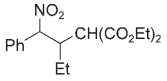
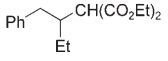
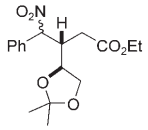
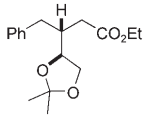
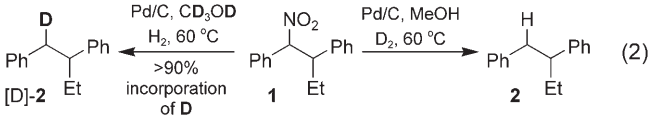
Table 2: Reductive cleavage of secondary benzylic nitroalkanes [Eq. (1)].

	Substrate		Product[a]		Yield [%]
1		**1**		**2**	89
2		**4**		**5**	91
3		**6**		**7**	95
4		**8**		**9**	94
5		**10**		**11**	92
6		**12**		**13**	81
7		**14**		**15**	91
8		**16**		**17**	73
9		**18**		**19**	68
10		**20**[b]		**21**	88[c]
11		**22**		**23**	81
12		**24**		**25**	50
13		**26**		**27**	64
14		**28**		**29**	78[d]

[a] Reaction conditions: 5–10 mol% $Pd(OH)_2/C$, EtOH, 1 bar H_2 (balloon), 70 °C. [b] Barua and co-workers obtained **20** in 80% yield and 90% *ee* by using the enantioselective Henry catalyzed by Ln as reported by Shibasaki and co-workers.[8a,11] [c] Only 5% of the parent diol was obtained. [d] Product **28** was obtained as a 10:1 separable mixture of diastereoisomers,[9] and the reaction was performed on a mixture (at the benzylic position) of the major isomer only. Bn = benzyl.

substrate with Pearlman's catalyst ($Pd(OH)_2/C$) in ethanol under H_2 at 70 °C cleanly afforded alkane products. Various neighboring functional groups and substitution patterns are tolerated. Nitroalkyne **10** (Table 2, entry 5) also reacted cleanly to give the fully saturated alkane **11**. This could be an interesting starting point for the synthesis of these building blocks, given the recent progress in the asymmetric addition of alkynes to nitroolefins reported by Tomioka and co-workers.[9] Benzylic nitro groups that are part of saturated rings were also reductively cleaved (Table 2, entry 6). Nitroalcohols, which can be obtained by Henry reaction of aryl nitromethane with aldehydes, are cleanly reduced to the corresponding homobenzylic alcohols (Table 2, entry 7). The presence of electron-donating and electron-withdrawing groups on the aryl ring is well tolerated (Table 2, entries 8 and 9, respectively). Interestingly, benzylic denitration of **20** was faster than deprotection of the *O*-benzyl ether, leading to a secondary homobenzylic alcohol. Esters (Table 2, entries 11 and 12), diesters (entry 13), as well as acetonides (entry 14) are compatible with the reaction conditions.[10]

To gain more insight into this process, we carried out some mechanistic studies [Eq. (2)]. When substrate **1** was treated

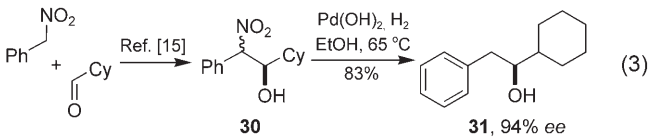


(2)

with Pd/C under a D_2 atmosphere, unexpectedly, we observed no deuterium incorporation in the product. This observation is inconsistent with either of two mechanistic possibilities: 1) the organonitro compound suffers elimination followed by reduction of the C=C bond, and 2) the formation of a hydrido organopalladium intermediate that undergoes reductive elimination. An additional control experiment was carried out to probe whether *N*-benzylamine **3** is an intermediate. Under otherwise identical conditions, **3** did not afford hydrocarbon **2** but was fully recovered from the reaction mixture.

We suspected that the solvent was the source of the benzylic hydrogen atom. In this respect, when the reaction was conducted in CD_3OD, we obtained monodeuterated product [D]-**2**.[12] Based on these observations, a mechanism can tentatively be proposed in which Pd^0 displaces the nitro electrofuge to furnish a benzylic organopalladium intermediate that undergoes protonation by the solvent. This is in contrast to the typical reaction of such intermediates in which the benzylic palladium species behaves as an electrophile.[13]

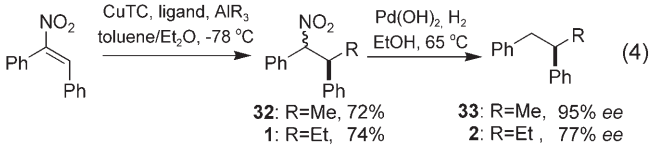
Beyond the mechanistic curiosities of this process, the fact that the nitro group can be effectively removed from a secondary benzylic site offers new possibilities for organonitro compounds prepared through asymmetric synthesis.[14] The potential for the implementation of such a strategy can be found in recent enantioselective Henry aldol reactions of phenyl nitromethane and various aldehydes using a guanidine thiourea catalyst, as reported by Nagasawa and co-workers.[15] We have applied this strategy in the synthesis of **31** [Eq. (3), Cy = cyclohexyl], which involves a Henry reaction and subsequent reductive cleavage of the nitro group in **30** to afford the homobenzylic alcohol with high enantiomeric



(3)

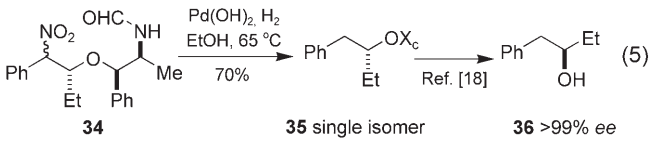
excess (94%). Thus, this sequence provides a convenient access to a large range of homobenzylic alcohols in optically active form. This result should stimulate additional development in asymmetric Henry reactions of aryl-substituted nitromethanes.

We have also examined the products of enantioselective conjugate additions to nitroolefins, a field which has lately witnessed rapid developments.[16] These processes are generally highly effective in controlling the stereoselectivity at the β-carbon atom which undergoes attack. However, not unexpectedly, they display a lack of selectivity at the carbon atom bearing the nitro group. We have carried out the conjugate addition of trimethylaluminum and triethylaluminum to β-nitrostyrene, as described by Polet and Alexakis, to give **1** and **32** [Eq. (4), CuTC = copper(I) thiophene-2-carboxylate].[16o] On exposure of **1** and **32** to the conditions for reductive cleavage, the corresponding optically active 1,2-diphenylalkanes **2** and **33** were isolated with high enantiomeric excesses (95 and 77% *ee*, respectively).[17]



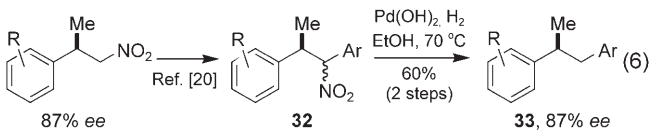
(4)

The addition of *N*-formylnorephedrine to (*E*)-(1-nitrobut-1-enyl)benzene following the procedure of Enders et al. for conjugate additions to nitroolefins provided **34** [Eq. (5), X_c = chiral auxiliary].[16a,c,af] Subsequent cleavage of the nitro group gave **35** as a single diastereomer in 70% yield, which was then shown to give **36** (99% *ee*).[18]



(5)

In an approach towards optically active nitro compounds, we have reported the enantioselective conjugate reduction of β,β-disubstituted nitroolefins using a chiral bisphosphine–Cu^I catalyst and silane.[19] In a separate, unrelated study, Buchwald and co-workers reported a Pd-catalyzed arylation of nitronates.[20] The combination of these two reactions allows access to compounds such as **32** [Eq. (6); R = H, Ar = Ph]. The lack of stereocontrol in the Pd-mediated coupling is of no consequence because subsequent reductive cleavage removes this functional group to give **33**.



(6)

In conclusion, we have reported that exposure of benzylic nitroalkanes to Pd/H_2 leads to heterolytic C–N bond reduction in good yields to give the parent alkanes. This reaction is noteworthy as it significantly expands the scope of building blocks, such as homobenzylic alcohols, that can be accessed. Thus, we have demonstrated the potential of the process by applying it to various modern methods for the asymmetric synthesis of nitroalkanes. It is important to note that the reductive removal of the nitro group occurs without loss of optical activity at adjacent centers. We have also proposed a possible mechanism for this transformation. The traceless removal of the nitro group after a host of modern asymmetric transformations involving nitro compounds leaves behind a stereogenic center that may otherwise not be easily installed.

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Keywords: cleavage reactions · nitro compounds · palladium · reduction · synthetic methods

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