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The direct reductive amination of electron-deficient amines with aldehydes: the unique reactivity of the Re_2O_7 catalyst†

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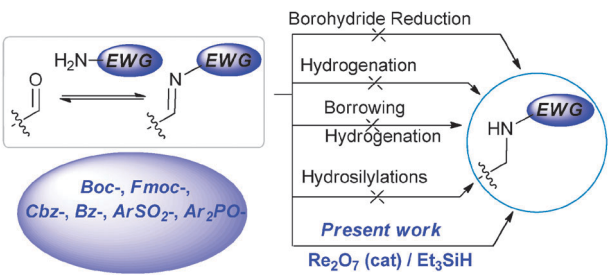
An unprecedented direct reductive amination of electron-deficient amines such as Cbz-, Boc-, EtOCO-, Fmoc-, Bz-, $ArSO_2$-, Ar_2PO-, *etc.* protected amines with aldehydes is achieved using the Re_2O_7 catalyst and silanes as the hydride source. Excellent regioselective mono-alkylation and chemo-selective reductive-amination were observed.

The primary amines or their protected analogues are crucial as synthetic tools for the synthesis of various natural products, pharmaceuticals, dyes, agrochemicals, and fine chemicals.[1] Among the primary amines, the terminal primary amines are the most useful, but their selective synthesis is challenging, due to their high reactivity.

The direct reductive amination (DRA) of aldehydes with ammonia or N-protected amines is one of the most attractive strategies for the synthesis of terminal primary amines or their protected analogues, respectively.[2] In general, the usage of N-protected amines is more successful as the amine counterpart compared to ammonia because of the problem of over-alkylation of terminal primary amines derived from ammonia.[3–10] Unfortunately, all the existing protocols for such DRA are *limited to the use of electron-rich amines [N-aryl or alkyl amines] only*; in particular, there is *literally no report for the same using useful electron-deficient amines [such as Boc-, Fmoc-, Cbz-, EtOCO-, Bz-, $ArSO_2$-, Ar_2PO-, etc. protected amines]* (Scheme 1). Even the reduction of preformed imines has been restricted to N-aryl imines.[11,12] Nevertheless, the tedious procedure of deprotection of the N-aryl or -alkyl group from the corresponding products limits their synthetic applications.[13]

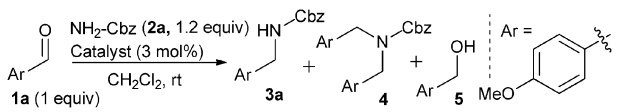


Scheme 1 Direct reductive amination (DRA) of aldehydes with electron-deficient amines.

Electron-deficient groups on nitrogen such as N-Boc, N-Cbz, N-Fmoc, N-CO_2Et, N-Bz, N-SO_2Ar, N-$POAr_2$, *etc.* are known to be the most useful protecting groups in organic synthesis and many of them can easily be cleaved.[13] However, the real challenge in the usage of such electron-deficient amines for DRA might be the difficulty in *in situ* imine formation[14] which might cause direct reduction to proceed in preference to reductive amination. Therefore, a milder catalyst aimed towards the reductive amination of the above-mentioned electron-deficient amines with aldehydes would be of major significance.

As part of our ongoing interest in the utilization of oxo-rhenium catalysts for organic transformation,[15] we found the unique reactivity of the Re_2O_7 catalyst for the current reductive amination of synthetically useful electron-deficient amines with excellent regio- and chemo-selectivity (Table 1). Recently, oxo-rhenium complexes in the high oxidation state have emerged as mild, non-toxic, and air/moisture stable catalysts for efficient hydrosilane activation[16] as well as various organic transformations.[17]

Table 1 Optimization of the reaction conditions



	Catalyst (3 mol%)	"H" source	*t*/h	3a[a]	4[d]	5[d]
1		$NaBH_4$[b]	1	0	—	100
2		$NaHB(OAc)_3$[b]	1	0	—	100
3	CF_3CO_2H (1.0 equiv.)	PMHS[c]	1	0	—	—
4	Bu_2SnCl_2	$PhSiH_3$[c]	12	0	—	—
5	$InCl_3$	$PhSiH_3$[c]	12	0	—	—
6	Ph_3PAuCl–AgOTf	H. E.[c,e]	12	0	—	—
7	MoO_2Cl_2	Et_3SiH[c]	12	15	—	—
8	$ReIO_2(PPh_3)_2$	Et_3SiH[c]	2	0	—	—
9	$ReCl_3O(PPh_3)_2$	Et_3SiH[c]	2	0	—	—
10	$ReCl_3O(SMe_2)PPh_3$	Et_3SiH[c]	2	0	—	—
11	$MeReO_3$ (MTO)	Et_3SiH[c]	0.5	10	—	5
12	Re_2O_7 (1.5 mol%)[f]	Et_3SiH[c]	0.5	96	<1	<1

[a] Yield of the isolated product. [b] MeOH was used as a solvent; 1.5 equiv. of reagent used. [c] 1.2 equiv. of silane used. [d] The % was determined by ^{1}H NMR of the reaction mixture. [e] H. E. = Hantzsch Ester. [f] See ref. 18 and 19.

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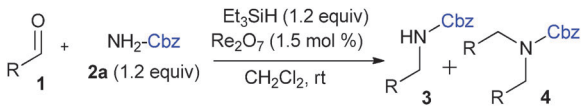
The various catalysts and/or reagents which have already been successful for DRA of electron-rich amines were screened by treatment of benzyl carbamate (**2a**) and *p*-MeO-benzaldehyde (**1a**) (summarized in Table 1). As shown, after a series of depressing failures using these traditional methods, we found the unique reactivity of the Re_2O_7 catalyst for the same. Interestingly, the reaction was completed within 30 min (96% isolated yield) with chemo- and regio-selective formation of the mono-alkylated product (**3a**) only (entry 12). Other solvents such as THF (0%), Et_2O (10%), toluene (14%), CH_3CN (86%) under similar conditions gave reduced conversion. With these optimized conditions in hand, we explored the scope of the reaction with different aldehydes **1b–w** (Table 2).

In general, different substituted aromatic aldehydes, except for acid, amine, and hydroxyl substitutions, provided the corresponding protected amines **3b–h** in very good to excellent yields (entries 1–9, Table 2). Heteroaromatic and α,β-unsaturated aldehydes also worked equally well (entries 10–13). Even the most challenging substrates such as straight chain aliphatic aldehydes **1o–t**, wherein over alkylation is generally a crucial problem, gave the corresponding mono-alkylated amines only (**3m–r**) (entries 14–19). The structurally sensitive aldehydes, such as cyclopropyl (**1u**) and ferrocenyl (**1v**) aldehyde, worked well (entries 20 and 21). Finally, the dimethyl acetal of benzaldehyde (**1w**) was tested and provided the corresponding amine with high yield (entry 22). *Notably, in all cases almost complete regioselectivity to the monoalkylated amine* **3** *was observed.*

Subsequently, we turned our attention toward the elaboration of the amines counterpart (Table 3). Amazingly, highly acid sensitive Boc- (**2b**), EtOCO- (**2d**), base sensitive Fmoc- (**2c**), and other electron-deficient functionalities including pTs- (**2e**), $PhSO_2$-(**2f**), Ph_2PO- (**2g**), PhCO- (**2h**) protected amines participate in DRA without any complication (entries 1–7, respectively). The electron-deficient secondary amines such as oxazolidone (**2i**) and isatin (**2j**) provided a high yield of corresponding N-benzylated-analogues **6h** and **6i** respectively (entries 8 and 9). However, the aromatic primary amines (**2k–l**) and electron rich amines such as indane (**2m**) and morpholine (**2n**) also worked equally well (entries 10–13). Unfortunately, the Cbz-protected hydrazine (**2o**) remained unreactive under the standard reaction conditions.

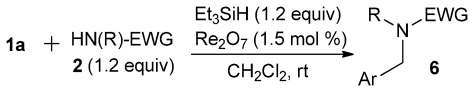
Table 2 Reductive amination of various aldehydes



	R (**1**)	*t*/h	**3** [a,b] (%)
1	Ph- (**1b**)	1	**3b**, 90
2	*p*-MeC_6H_5- (**1c**)	2	**3c**, 87
3	*p*-$Br\text{-}C_6H_5$- (**1d**)	1	**3d**, 88
4	*p*-$F\text{-}C_6H_5$- (**1e**)	0.5	**3e**, 88
5	*p*-$NO_2\text{-}C_6H_5$- (**1f**)	24	**3f**, 79
6	*p*-$CN\text{-}C_6H_5$- (**1g**)	4	**3g**, 64
7	*p*-$HO_2C\text{-}C_6H_5$- (**1h**)	24	—
8	*p*-$NH_2\text{-}C_6H_5$- (**1i**)	24	—
9	*o*-$HO\text{-}C_6H_5$- (**1j**)	24	**3h**, 18
10	2-Thiophenyl- (**1k**)	0.5	**3i**, 99
11	α-Naphthyl- (**1l**)	2	**3j**, 95
12	Cinnamyl- (**1m**)	1	**3k**, 97
13	Ph-C≡C- (**1n**)	12	**3l**, 73
14	Cyclohexyl- (**1o**)	1	**3m**, 98
15	Octyl- (**1p**)	2	**3n**, 98
16	*n*-Butyl- (**1q**)	0.5	**3o**, 94
17	Ethyl- (**1r**)	0.5	**3p**, 94
18	Bn- (**1s**)	1	**3q**, 97
19	$PhCH_2CH_2$- (**1t**)	1.5	**3r**, 99
20	Cyclopropyl- (**1u**)	1	**3s**, 98
21	Ferrocenyl- (**1v**)	24	**3t**, 69
22	$PhCH(OMe)_2$ (**1w**)	3	**3b**, 85

[a] Yield of the isolated product. [b] No trace of **4** was detected on TLC and the ratio was confirmed by ^1H NMR of the reaction mixture.

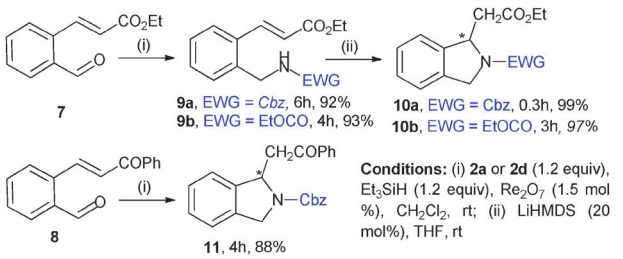
Table 3 Reductive amination of various amines



	EWG-(R)NH, **2**	*t*/h	R	**6** [a] (%)
1	Boc-NH_2 (**2b**)	12	H	**6a**,76
2	Fmoc-NH_2 (**2c**)	6	H	**6b**, 92
3	EtOCO-NH_2 (**2d**)	1	H	**6c**, 95
4	pTs-NH_2 (**2e**)	12	H	**6d**, 74
5	$PhSO_2$-NH_2 (**2f**)	12	H	**6e**, 50
6	$Ph_2P(O)$-NH_2 (**2g**)	12[b]	H	**6f**, 68
7	PhCO-NH_2 (**2h**)	12	H	**6g**, 71
8	Oxazolidone (**2i**)	24	—	**6h**, 60
9	Isatin (**2j**)	12[c]	—	**6i**, 65
10	Ph-NH_2 (**2k**)	1[b]	H	**6j**, 81
11	*p*$NO_2\text{-}C_6H_4$-NH_2 (**2l**)	20[b]	H	**6k**, 67
12	Indane (**2m**)	12[b]	—	**6l**, 93
13	Morpholine (**2n**)	24[b]	—	**6m**, 83
14	Cbz-$NHNH_2$ (**2o**)	24	—	—

[a] Yield of the isolated product after column chromatography. [b] $PhSiH_3$ was used in THF under reflux. [c] PhCHO (**1b**) used as the aldehyde.

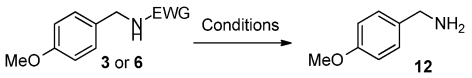
Next, the DRA of *ortho* electron-deficient vinyl substituted arylaldehydes with amines (**2a** and **2d**) was demonstrated (see Scheme 2). Interestingly, in the case of *o*-formylcinnamate (**7**), only the reductive amination products **9a–b** were obtained, keeping the cinnamate functionality unaffected. Further, on treatment of **9a–b** with catalytic LiHMDS, the substituted isoindoline **10a–b** were obtained in excellent yields *via* the conjugate addition reaction. On the other hand, the *o*-formylchalcone (**8**) proceeded to produce the functionalized isoindoline **11** directly *via* a cascade reductive amination and conjugate addition pathway. Thus, a new stereocenter was generated *via* a sequential reductive amination–conjugate addition strategy.



Scheme 2 Reductive amination–conjugate addition reactions.

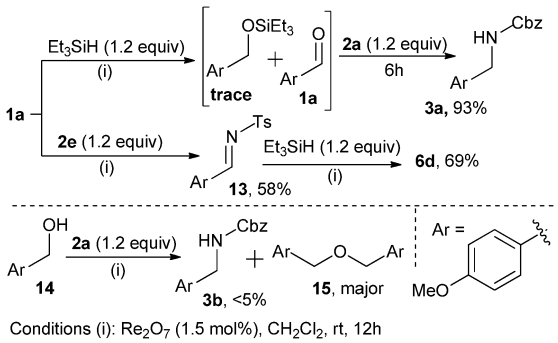
Surprisingly, the treatment of ketones such as cyclohexanone, adamantanone and 5-nonanone under these conditions with amine (**2a**) did not provide the corresponding amine *via* DRA.

Table 4 Deprotection to free-primary amines



	3 or 6	Conditions	t/h	**12** (conversions)[a]
1	**3a**	**A**	6	Quantitative
2	**6a**	**B**	1	Quantitative
3	**6b**	**C**	2	Quantitative

A: in 6 N HCl solution, reflux; **B**: in 20% CF_3CO_2H in CH_2Cl_2, rt; **C**: 20% piperidine in DMF, rt. [a] Conversions were determined by ^{1}H NMR spectroscopy using acetophenone as an internal standard.



Scheme 3 Reduction followed by substitution *vs*. DRA.

Finally, the easy de-protection of synthesized protected amines was carried out to provide free primary amines (see Table 4).

To gain further insight into the mechanism of this Re_2O_7 catalysis, we performed the following reactions. As shown in Scheme 3, under these conditions, the current reaction proceeded through the reductive-amination pathway (*e.g.*, formation of imine, followed by reduction using *in situ* formed [H-Re] species[12,16]) only, not *via* reduction followed by the substitution process.

In conclusion, we have reported that the Re_2O_7-catalyst is capable of promoting the reductive amination of electron-deficient amines with aldehydes. The reaction proceeded in an excellent chemo- and regio-selective manner. The sequential and cascade reductive amination–conjugate addition to provide derivatives of isoindoline, containing a chiral center, has also been exemplified. Finally, the easy deprotection of the corresponding products to free terminal primary amines has also been carried out. Further utilization of oxo-rhenium complexes for reductive amination of ketones is in progress.

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18 Different sources of Re_2O_7 as well as different purity levels provided the similar reactivity (see ESI†).

19 The trace analysis of Re_2O_7 using the ICP-OES technique, the major contaminants detected [ppm]: Co (0.14), Cu (0.72), Fe (3.7). But, the current DRA using ppm level of these catalysts (such as $CoCl_2$, $CuBr_2$, and $FeCl_3$) in the absence of Re_2O_7 was not positive. This ruled out the possibility of current catalysis by trace impurities in Re_2O_7.

