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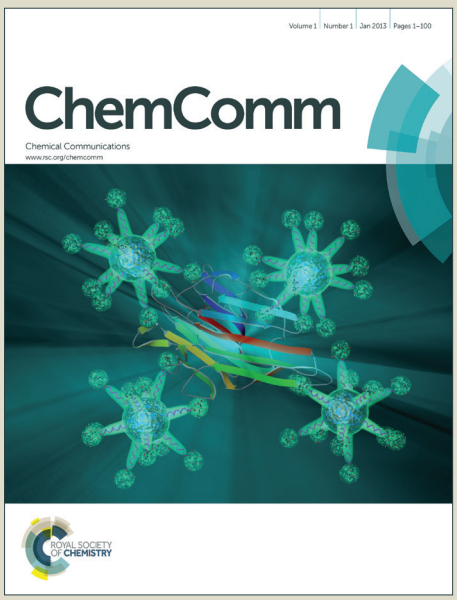

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Chemoselective Reduction of α-Keto Amides by Nickel Catalyst

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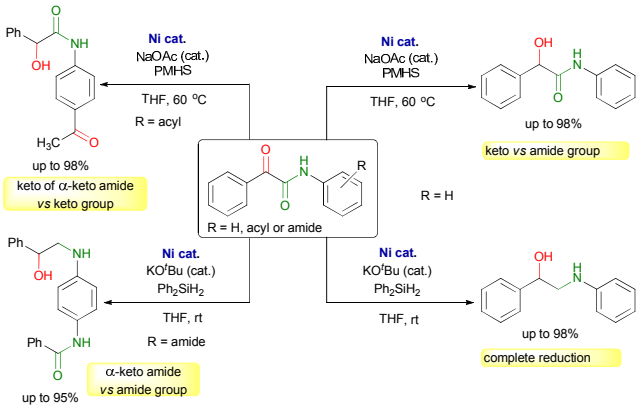
Ni-catalysts are used for the first time to synthesize highly important α-hydroxy amides and β-amino alcohols from α-keto amides by chemoselective and complete reduction using hydrosilanes. Chemoselective complete reduction of α-keto amides in the presence of simple amide group is a key benefit of this Ni-catalyst.

α-Hydroxy amides and β-amino alcohols are very important building blocks in pharmaceutical industry and show several biological activities such as anticonvulsant action,[1] bronchospam, bradycardia and peripheral vascular resistance.[2] Both these compounds can be easily obtained from α-keto amides by chemoselective reduction of keto group and complete reduction of both keto and amide groups respectively. A challenging task arises for selective reduction of α-keto amides as both the keto and amide groups are present there. Although ketone reduction is well established by hydrosilane,[3] reduction of readily available but less reactive carboxylic amide to amine is one of the simplest less explored methodologies in organic chemistry. The traditional reducing agents such as $LiAlH_4$ and hydroboranes have limitations like less chemoselectivity, moisture sensitive, expensive and tedious purification process.[4] Catalytic hydrogenation[5] should be the appropriate alternative, but there is no general method available for the selective amide reduction.

Recently, considerable progress has been made in the field of amide reduction using hydrosilanes in the presence of metal catalysts. Initial reports used metal catalysts like Rh,[6] Ru,[7] Pd,[8] Pt,[9] Ir[10] etc.[11] Later, other metal catalysts such as Fe,[12] Cu,[13] and Zn[14] were brought in to action. In addition, there are reports of tertiary amides reduction using KOH[15] and TBAF[16] catalyst but reduction of secondary amides are difficult.[17] Even though there are reports available for ketone reduction by economic and readily available Ni[18] catalyst and hydrosilanes, but carboxylic amide to amines is yet to be reported. Herein for the first time we report an efficient Ni catalyst for the chemoselective reduction of α-keto amides to α-hydroxy amides and complete reduction to β-amino alcohols. The advantage of this Ni catalyst is that it can selectively reduce keto group of α-keto amides in the presence of simple keto functional group and its ability to reduce both keto and amide groups of α-keto amides in the presence of other amide functional group (Scheme 1).

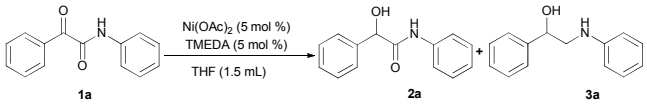


Scheme 1. Chemoselective reduction of α-keto amides by Ni catalyst.

Initially, 2-oxo-*N*-2-diphenylacetamide **1a** was taken as the model substrate and the reduction was carried out using various nickel salts with tetramethylethylene diamine (TMEDA) ligand and $(EtO)_3SiH$ at room temperature. The reaction took place in the case of Ni acetate and 32% of α-hydroxy amides **2a** were obtained. Further optimization was carried out with $Ni(OAc)_2$ after screening NaO^{t}Bu and KO^{t}Bu bases as additives, 10 mol % of KO^{t}Bu was found to be the appropriate additive as it yielded a mixture of 82% of **2a** and 8% of **3a** (Table 1, entry 2). In order to increase the efficiency of the reaction towards **2a**, temperature was increased to 60 °C. Although the reaction time was reduced, the selectivity also reduced (entry 3). To increase the selectivity, mild hydrosilanes such as polymethyl hydrosilane (PMHS) was used as we expected, the

selectivity was increased and only **2a** was obtained with 98% of isolated yield (entry 4). The same reaction without base worked equally well but the reaction time was 24 hours (entry 5). The rate of the reaction was increased by adding 10 mol% of NaOAc as an additive (entry 6). The additive (acetate ion) may help to release the hydride ion from the PMHS which may be the reason for the fast reaction rate. The same reaction without catalyst did not give any reaction (entry 7).

Table 1. Optimization of chemoselective reduction of α-keto amides by Ni catalyst[a]

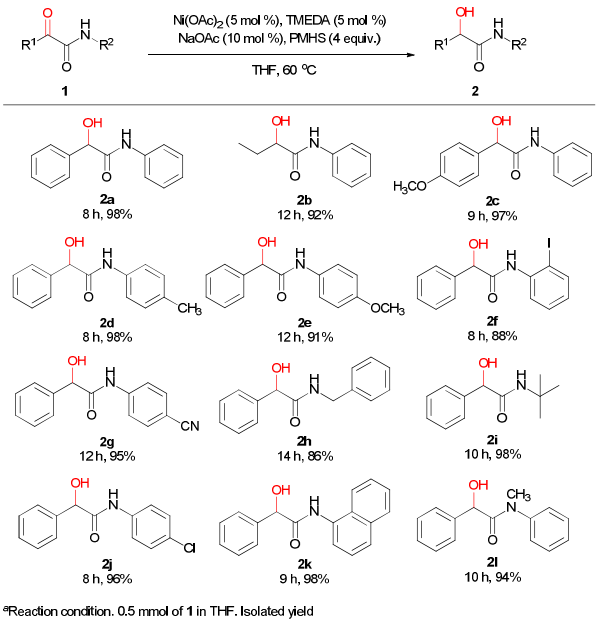


1a 2a 3a

entry	silane (equiv.)	additive (10 mol %)	temp (°C)	time (h)	yield(%)[b] 2a	3a
1	$(EtO)_3SiH$ (2)	NaO^{t}Bu	rt	48	78	6
2	$(EtO)_3SiH$ (2)	KO^{t}Bu	rt	48	82	8
3	$(EtO)_3SiH$ (2)	KO^{t}Bu	60	10	58	18
4	PMHS (4)	KO^{t}Bu	60	12	98	-
5	PMHS (4)	-	60	24	95	-
6	**PMHS (4)**	**NaOAc**	**60**	**8**	**98**	**-**
7[c]	PMHS (4)	NaOAc	60	24	-	-
8	$(EtO)_3SiH$ (4)	KO^{t}Bu	60	24	10	78
9	Ph_3SiH (4)	KO^{t}Bu	rt	24	81	16
10	TMDSO (4)	KO^{t}Bu	rt	24	21	74
11	**Ph_2SiH_2 (4)**	**KO^{t}Bu**	**rt**	**12**	**-**	**97**
12[c]	Ph_2SiH_2 (4)	KO^{t}Bu	rt	12	38	8
13[d]	Ph_2SiH_2 (4)	KO^{t}Bu	rt	24	30	10
14[d]	PMHS (4)	NaOAc	60	24	11	-
15[e]	Ph_2SiH_2 (4)	KO^{t}Bu	rt	24	36	13
16[e]	PMHS (4)	NaOAc	60	24	-	-
17	Ph_2SiH_2 (4)	-	60	24	90	-

[a]Reaction condition. 0.5 mmol of **1a** in THF. [b]Isolated yield. [c]With out $Ni(OAc)_2$ and ligand. [d]Without TMEDA. [e]Without $Ni(OAc)_2$.

Table 2. Chemoselective reduction of keto group of α-keto amides by $Ni(OAc)_2$-TMEDA catalyst[a]

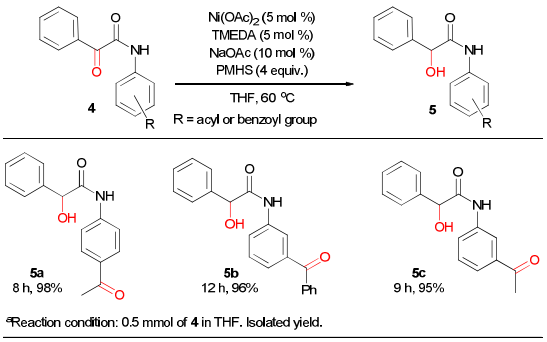


[a]Reaction condition. 0.5 mmol of **1** in THF. Isolated yield

To show the scope of the Ni catalyzed chemoselective reduction of α-keto amides, several α-keto amides were examined and the results are summarized in Table 2. Substitution like electron donating groups (**2d** and **2e**), electron withdrawing groups (**2f**, **2j** and **2g**) in the amide nitrogen attached aromatic ring and aliphatic amide attached ketone (**2i** and **2h**) were well tolerated. It is important to note that other sensitive functional groups to reduction reaction such as nitrile and halo groups are unaffected.

We were curious to know the reactivity of keto group of **1a** in the presence of externally added ketone like benzophenone and in this reaction we have isolated quantitative amount of un reacted benzophenone along with 95% of α-hydroxy amide. When a substrate such as **4**, having isolated keto group and α-keto amide treated with Ni catalyst, the α-keto amide chemoselectively yielded **5** without affecting the isolated ketone (Table 3). Few more substrates were examined similar to **4** and the results are summarized in Table 3. In this chemoselective reduction, the α-keto amide's keto group should be more electrophilic than isolated ketone due to the presence of electron withdrawing α-amide. In addition to this, the nitrogen atom of α-keto amide should play a vital role by co-ordinating with nickel hydride as directing group for α-keto group reduction.

Table 3. Chemoselective reduction of keto group of α-keto amide by Ni catalyst in the presence of other keto functional groups[a]

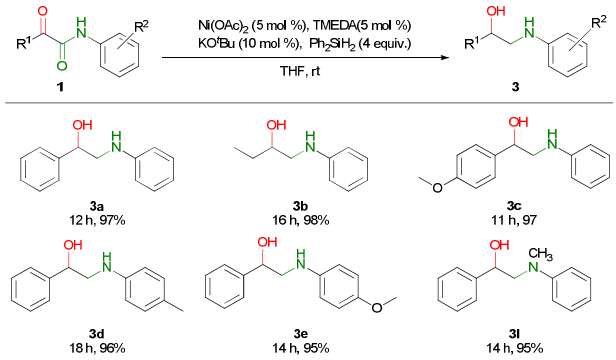


[a]Reaction condition: 0.5 mmol of **4** in THF. Isolated yield.

After achieving an appropriate optimized reaction conditions for chemoselective reduction of α-keto amide **1a** to get **2a**, we shifted our focus to complete reduction of **1a** to yield β-amino alcohol **3a**. Initially, we have increased the quantity of $(EtO)_3SiH$ to 4 equivalents. As expected, this reaction gave complete reduction product **3a** as major (Table 1, entry 3 vs 8). In the case of Ph_3SiH, the reaction gave very poor yield of **3a** (16%) as minor product (entry 9), whereas in the case of tetramethyldisiloxane (TMDSO) the reaction gave 74% of **3a** as a major product (entry 10). Usage of stronger reducing agent Ph_2SiH_2 yielded only complete reduction product **3a** with 97% of isolated yield (entry 11). The same reaction without $Ni(OAc)_2$ and ligand, gave a series of spots in the TLC and we isolated 38% of **2a** and 8% of **3a** along with 15% of aniline and 10% of benzoyl formic acid as a by-products (entry 12). To know the ligand role, two reactions were carried out without ligand, only in the presence of $Ni(OAc)_2$ along with KO^{t}Bu. The reaction yielded 30% of **2a** and 10% of **3a**. In the case of NaOAc, the reaction yielded only 11% of **2a** (entry 13 and 14). Similarly, to know the role of metal salt in the reduction, blank reactions were carried only

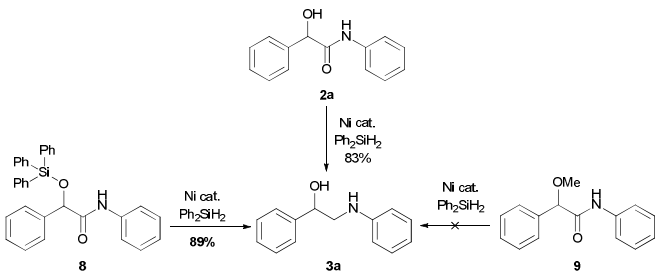
with TMEDA and additives. In the case of KO^{t}Bu, the reaction yielded 36% of **2a** and 13% of **3a** along with aniline and benzoylformic acid as side products. But in the case of NaOAc, there is no reaction (entry 15 and 16). To understand the role of base in complete reduction, blank reaction was carried without KO^{t}Bu and the reaction did not give complete reduction product **3a** (entry 17). To establish the substrate scope of complete reduction of α-keto amide, several α-keto amides were reduced with Ph_2SiH_2 and 10 mol% of KO^{t}Bu at room temperature using 5 mol% of Ni catalyst and the results are summarized in Table 4. Electron donating groups on α-keto amides (**3c**, **3d** and **3e**) and aliphatic ketone attached amide (**3b**) were well tolerated. Only aromatic amide attached ketones are getting reduced under the optimized reaction condition.

Table 4. Complete reduction of both keto and amide groups of α-keto amides by Ni catalyst[a]



[a]Reaction condition. 0.5 mmol of **1a** in THF. Isolated yield.

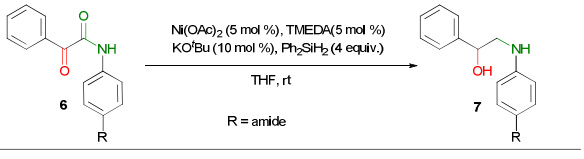
When N-phenylbenzamide and phenyl(piperidin-1-yl)methanone were added to α-keto amide **1a** under complete reduction conditions, only **1a** reduced to yield 95% of β-amino alcohol **3a**. Then we synthesised diamide such as **6a** containing simple carboxylic amide and α-keto amide. Then **6a** was treated with Ni catalyzed complete reduction conditions, and α-ketoamide functional group got reduced without affecting the isolated amide to yield **7a**. To show the substrate scope of this chemoselective reduction of amide-ketoamide, a series of amide-ketoamides were synthesized (Table 5, **6a**-**6e**). In all the reactions, only the α-keto amide functional group got reduced without affecting the isolated amide (**7a**-**7e**) with quantitative yields. Highly reactive tertiary amides and benzyl amide were well tolerated under the same reduction conditions (**7b**, **7c** and **7d**).

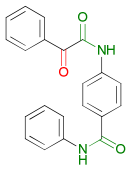
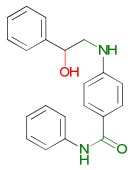
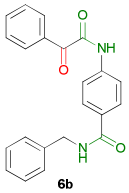
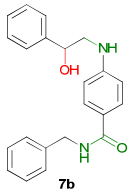
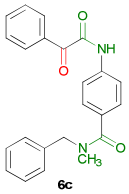
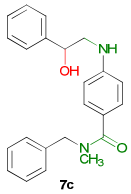
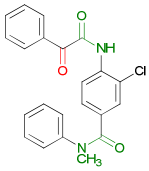
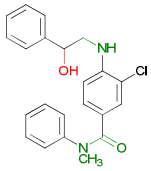
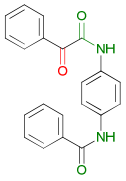
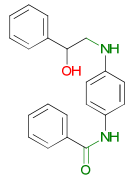


Scheme 2. Reduction of α-hydroxy amides and its ether derivatives

Generally, keto group is more reactive than carboxylic amide for the reduction reaction. In case of amido-ketoamide **6a**, we assume that first the keto group will be chemoselectively reduced to α-hydroxy amide **2a** as intermediate. The resulting **2a** will co-ordinate with nickel hydride to reduce the α-keto amide's amide functional group which will not be possible in the case of isolated amides.

Table 5. Selective reduction of α-keto amides in the presence of isolated amide functional groups by Ni catalyst[a]



entry	6	7	time (h)	yield[b] (%)
1	 6a	 7a	20	92
2	 6b	 7b	18	90
3	 6c	 7c	12	95
4	 6d	 7d	20	90
5	 6e	 7e	18	92

[a]Reaction condition: 0.5 mmol of **6** in THF. [b]Isolated yield.

To check this hypothesis, we used α-hydroxy amide **2a**, triphenylsilane protected hydroxy amide **8** and α-methoxy amide **9** for the complete reduction condition. **2a** and **8** yielded amide reduced product 83% and 89% respectively. As we expected, α-methoxy amide **9** did not yield even trace amount of reduced product which shows that the α-hydroxy group of α-keto amide plays a crucial role in the amide reduction of α-keto amide (Scheme 2).

However the detailed mechanistic study of this nickel catalyzed reduction and its applications are under progress.

Conclusions

In conclusion, for the first time we have developed an efficient Ni-TMEDA catalyst for the chemoselective reduction of ketone of α-keto amides to yield α-hydroxy amide and complete reduction of α-keto amides to provide β-amino alcohols using appropriate silanes. Although metal catalysts such as Rh, Zn, Cu, Fe, Co, Ti, Ru, etc. are known to reduce the keto group and metal catalysts such as Rh, Ru, Pd, Pt, Ir, Fe, Cu, Zn, etc. are known to reduce amide group, but Ni is the first metal salt used for the chemoselective reduction of keto group of α-keto amides in presence of other ketone functional groups and chemoselective complete reduction of α-keto amide in the presence of other amide functional groups.

Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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