

Direct One-Pot Reductive N-Alkylation of Nitroarenes by using Alcohols with Supported Gold Catalysts

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The formation of C–N bonds is one of the most important transformations in chemistry because nitrogen-containing compounds, particularly amines and their derivatives, are versatile building blocks for various organic molecules and essential precursors to a variety of biologically active compounds.^[1] Although several methods are known for the synthesis of C–N bonds,^[2] preparation under mild and waste-free conditions using simple, inexpensive, and readily available feedstock is still a challenging goal. The transition-metal-catalyzed coupling of amines with alcohols by using a hydrogen-borrowing strategy^[3] (also known as a hydrogen-autotransfer process) has proven to be an atom-economical and environmentally attractive method for the construction of C–N bonds, especially for secondary amine preparation. Although many efficient catalysts for such transformations have been reported,^[3e–f,4] the development of easily recoverable and recyclable heterogeneous catalysts that can solve the problem of the homogeneous systems has attracted special attention. To the best of our knowledge, few heterogeneous catalyst systems^[5] have been reported that enable efficient and selective N-alkylation of amines with alcohols under simple, mild, and environmentally benign conditions.

Nitroarenes are cheap and readily available organic compounds and the reduction of nitro compounds is a key step in the preparation of many pharmaceutical agents and fine chemicals.^[6] Despite numerous established procedures for the reduction of nitro compounds,^[7] the development of catalytic methodologies that afford high chemo- and regioselectivity under mild reaction conditions is still a challenging problem.^[8] As for the synthesis of secondary amines, the direct use of commercially available and inexpensive nitroarenes and alcohols as starting materials is highly attractive, especially when a single catalyst system could be employed. In this valuable one-pot multistep transformation, the alcohol may conceivably serve two possible functions: as the hy-

drogen source for nitro reduction and as the alkylating reagent based on the catalytic hydrogen transfer. Although excess alcohol is required to ensure the completion of the reaction^[9] (see the Supporting Information for possible reaction stoichiometries), the operational simplicity of such transformations may have practical advantages for a concise synthesis of N-substituted amines in a more straightforward manner. Compared to the great progress being made in the amination of amines with alcohols,^[10] there are scarcely available reports dealing with the direct amination of nitroarenes with alcohols. To date, only three Ru-based homogeneous systems have been reported.^[11] However, these homogeneous catalysts are problematic in terms of the recovery/recycling of the catalyst and the necessity of special handling of metal complexes. From a sustainable point of view, a more efficient reaction with a ligand-free heterogeneous catalyst is highly desired.

Over the last five years, we have been interested in the unique catalytic properties of supported gold nanoparticles (NPs) and involved in their application to sustainable organic synthesis.^[9e,12] Recently, we have shown that very small Au NPs (approx. 1.8 nm) deposited on TiO₂ (Au/TiO₂-VS; VS=very small) acts as an efficient heterogeneous catalyst for the clean and atom-efficient mono-N-alkylation of a range of amines with alcohols in excellent yields under hydrogen-borrowing conditions.^[12a] In view of the prominent efficiency of the gold system for the amination of amines with alcohols, we envisioned that the Au-mediated hydrogen-borrowing strategy could afford a green and efficient protocol for the direct amination of nitroarenes with alcohols under mild conditions. Herein, we report for the first time that the simple Au/TiO₂-VS system can catalyze the selective secondary or tertiary amine formation from the direct condensation of nitroarenes and alcohols. Notably, the reaction can proceed effectively under ligand- and base-free conditions without any external hydrogen resources. To the best of our knowledge, this study also forms the first report of a one-pot selective preparation of imines from nitroarenes and alcohols by using a heterogeneous gold-mediated “catalytic hydrogen-transfer” procedure.

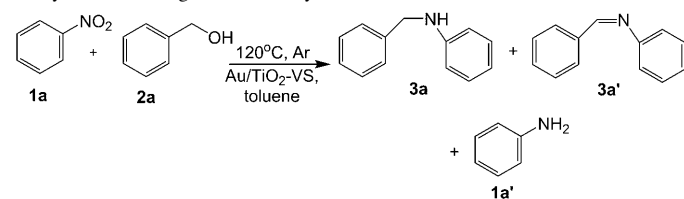
Based on our previous results in heterogeneous Au-catalyzed amine/alcohol coupling chemistry,^[12a] the optimization study was initiated with the direct amination of nitrobenzene (**1a**) with eight equivalents of benzyl alcohol (**2a**) in the presence of Au/TiO₂-VS (0.5 mol% of Au, see the Sup-

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porting Information) for 14 h at 120 °C under argon atmosphere. The results showed that the corresponding secondary amine, *N*-phenylbenzylamine (**3a**) was the main C–N cross-coupling product (Table 1). The initial rate of formation of **3a** was also measured under conditions in which conversion was below 30 % (result not shown). As observed with other

Table 1. Direct synthesis of secondary amine from nitrobenzene and benzyl alcohol using various catalysts.^[a]



Entry	Catalyst	Conversion [%] ^[d]	Selectivity [%] ^[d]		
			3a	3a'	1a'
1 ^[b]	Au/TiO ₂ -VS	100	> 99	–	–
2 ^[c]	Au/TiO ₂ -VS	100	96	4	–
3 ^[d]	Au/TiO ₂	100	70	17	13
4 ^[d]	Au/Al ₂ O ₃	100	20	49	31
5 ^[d]	Au/ZnO	100	13	62	25
6 ^[d]	Au/Fe ₂ O ₃	100	22	38	40
7	Au/CeO ₂	100	20	56	34
8	Au/ZrO ₂	100	54	26	20
9	Pd/TiO ₂	100	43	40	17
10	Ru/TiO ₂	100	18	76	6
11	TiO ₂	trace	–	–	–

[a] Reaction conditions: nitrobenzene (1 mmol), benzyl alcohol (8 mmol), toluene (1 mL), and catalyst (metal: 0.5 mol %) at 120 °C for 14 h under argon (Ar) atmosphere. [b] Trace amount of tertiary amine was detected (below 1 % yield). [c] Fifth run. [d] Au/TiO₂ and Au/Fe₂O₃ provided by World Gold Council (WGC). Au/Al₂O₃ and Au/ZnO provided by Mintek. [e] Selectivity based on nitrobenzene conversion, determined by GC using *n*-dodecane as the internal standard. Meanwhile, the benzyl alcohol that was present in eightfold excess also gives appreciable amounts of dehydrogenative byproducts including benzaldehyde and benzyl benzoate.

gold-catalyzed processes,^[9e, 12a–e] both the nature of the support and the particle size have a strong influence on the activity of the Au catalysts (Table 1, entries 1–8). Among the various supported gold catalysts tested, Au/TiO₂-VS gave the best results, with the highest yield of **3a** and the highest reaction rate (Table 1, entries 1–8). Of yet further interest is that this catalyst can be reused at least five times and still maintains a complete conversion of **1a** to give **3a** in yields of up to 96 % (Table 1, entry 2). No formation of **3a** was observed in the presence of Au-free TiO₂ (Table 1, entry 11). Under the conditions described in Table 1, Pd or Ru NPs supported on TiO₂ were not effective (Table 1, entries 9 and 10), illustrating that gold is far superior to other noble metals for the direct reductive mono-*N*-alkylation of **1a** with **2a**.

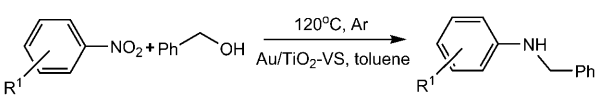
Subsequently, the reaction conditions were optimized with the Au/TiO₂-VS catalyst through variation of the solvents, temperature, and the **2a/1a** ratio (see Table S1 in the Supporting Information). First, the nature of solvents was inves-

tigated. Of the various solvents screened for this reaction, toluene was shown to be the solvent of choice (Table S1, entries 1–4). In toluene, the reaction rate increased as the temperature was raised from 80 to 120 °C (Table S1, entries 4–6). Studies on the effect of the molar ratio of **2a** to **1a** revealed that the reaction of **1a** with eight equivalents of **2a** gave the best results (see the Supporting Information, Table S1, entries 4, and 7–11). The use of three equivalents of **2a** led to incomplete conversion of **1a**, and only a trace amount of the desired secondary amine could be obtained (see the Supporting Information, Table S1, entry 7). Upon increasing the **2a/1a** ratio from three to eight, the reaction proceeded to completion along with a significant increase in the yield of the product **3a** (see the Supporting Information, Table S1, entries 4, 7, and 9). This result suggests that the composition of the reaction medium was critical for the desired reaction pathway. However, lower yields were observed when 10 or 15 equivalents of **2a** were employed (see the Supporting Information, Table S1, entries 10 and 11). It is noted that under optimized conditions, the use of five equivalents of **2a** can afford the selective formation of *N*-benzylideneaniline (**3a'**) with a high yield well above 95 % (see the Supporting Information, Table S1, entry 8). As imines are highly versatile synthetic intermediates for dyes, fragrances, pharmaceuticals, fungicides, and agricultural chemicals,^[13] the reaction chemistry described here may also provide new possibility to develop versatile heterogeneous catalysts for the tandem synthesis of imines through a direct conversion of nitroarenes with alcohols.

With suitable reaction conditions established, the scope of the Au/TiO₂-VS catalyzed reductive mono-*N*-alkylation with respect to nitrobenzene derivatives and alcohols was explored. As revealed in Table 2, various structurally diverse nitroarenes, regardless of the presence of electron-withdrawing or donating functional groups, could be mono-alkylated with **2a** to give the corresponding secondary amines in excellent yields. Relative to the direct coupling of substituted anilines and benzyl alcohol over Au/TiO₂-VS, the substituent at different positions on the nitroarenes affected the reaction rate significantly. For example, a much longer reaction time is required for reaction completion when *para*-methoxynitrobenzene was used as a substrate (Table 2, entry 3). The reaction tolerates the presence of halogens (Table 2, entries 4–7 and 9); however, a lower yield was obtained when the substituent was changed from fluoride to bromide, partially due to the poor solubility of substrate^[11a] (Table 2, entries 4–6). In the transformations of chloronitroarenes, the lower reaction rate of *o*-chloronitrobenzene relative to *meta* and *para* analogues indicated a steric effect (Table 2, entries 5, 7, and 9). Notably, reducible functional groups such as alkene and ketone, as well as ester moieties, remained intact during the reductive mono-*N*-alkylation process (Table 2, entries 10–12), demonstrating the high versatility of the present methodology for secondary amine synthesis.

Furthermore, the reaction also proceeds successfully with other structurally and electronically diverse alcohols

Table 2. Catalytic reaction of nitroarenes with benzyl alcohols.^[a]



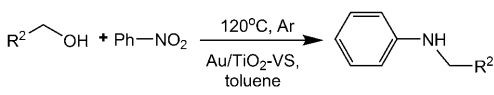
Entry	R ¹	Product	<i>t</i> [h]	Yield [%] ^[b]
1	H	Ph-NH-CH ₂ -Ph	14	> 99
2	<i>p</i> -Me	<i>p</i> -MePh-NH-CH ₂ -Ph	28	95 (92)
3	<i>p</i> -MeO	<i>p</i> -MeOPh-NH-CH ₂ -Ph	33	96
4	<i>p</i> -F	<i>p</i> -FPh-NH-CH ₂ -Ph	32	95
5	<i>p</i> -Cl	<i>p</i> -ClPh-NH-CH ₂ -Ph	32	93 (90)
6	<i>p</i> -Br	<i>p</i> -BrPh-NH-CH ₂ -Ph	36	86
7	<i>o</i> -Cl	<i>o</i> -ClPh-NH-CH ₂ -Ph	33	89 (84)
8	<i>m</i> -Me	<i>m</i> -MePh-NH-CH ₂ -Ph	25	98
9	<i>m</i> -Cl	<i>m</i> -ClPh-NH-CH ₂ -Ph	27	92 (90)
10	<i>p</i> -MeCO	<i>p</i> -MeCOPh-NH-CH ₂ -Ph	24	83
11	<i>p</i> -MeCO ₂	<i>p</i> -MeO ₂ CPh-NH-CH ₂ -Ph	35	76
12	<i>p</i> -CH ₂ =CH	<i>p</i> -CH ₂ =CH-Ph-NH-CH ₂ -Ph	28	94 (91)

[a] Reaction conditions: nitroarenes (1 mmol), benzyl alcohol (8 mmol), toluene (1 mL), catalyst (Au/TiO₂-VS, metal: 0.5 mol %), 120°C, under argon atmosphere. [b] Yields based on nitroarenes, determined by GC using *n*-dodecane as the internal standard. Numbers in parenthesis refer to yields of isolated products.

(Table 3). Alcohols with halogens reacted smoothly with nitrobenzene to give the corresponding products in good yields (Table 3, entries 5–7). Again, a bromide substituent dramatically decreased the reaction rate, and a prolonged reaction time of 36 h was needed for obtaining a high yield of the desired product when *p*-bromobenzyl alcohol was used as a substrate (Table 3, entry 5). The substituent at the *ortho* position has a great impact on the reaction; a moderate yield was obtained when *o*-chlorobenzyl alcohol, *o*-methoxybenzyl alcohol, or *o*-methylbenzyl alcohol was used (Table 3, entries 8–10). The Au/TiO₂-VS catalyst also shows promise for direct coupling of nitrobenzene with simple aliphatic alcohols under similar conditions (Table 3, entries 11–12). The notoriously difficult secondary alcohols (Table 3, entries 2 and 12) were successfully converted without any additives, which has no precedent in the literature. It is again noteworthy that the reaction of 2-phenethyl alcohol with nitrobenzene can afford a highly valuable 2-phenylethanamine derivative (Table 3, entry 1), a common structural feature found in many medicinal drugs such as Piriton^[14] and Tripeleminamine.^[15]

Given that the reductive mono-*N*-alkylation of nitrobenzene proceeded smoothly, we have explored the applicability of this protocol to tertiary amine formation through direct amination of various nitrobenzene derivatives by using alco-

Table 3. Catalytic reaction of nitrobenzene with various alcohols.^[a]

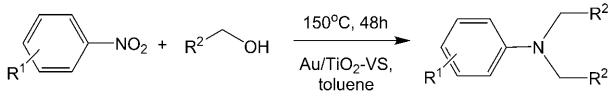


Entry	R ²	Product	<i>t</i> [h]	Yield [%] ^[c]
1	C ₆ H ₅ CH ₂	C ₆ H ₅ -CH ₂ -NH-Ph	21	91
2 ^[c]	C ₆ H ₅ (CH ₃)	C ₆ H ₅ -CH(CH ₃)-NH-Ph	35	87 (85)
3	<i>p</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄ -NH-Ph	18	97 (95)
4	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄ -NH-Ph	20	93
5	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄ -NH-Ph	36	88
6	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄ -NH-Ph	33	85 (83)
7	<i>p</i> -FC ₆ H ₄	<i>p</i> -FC ₆ H ₄ -NH-Ph	27	90
8	<i>o</i> -MeC ₆ H ₄	<i>o</i> -MeC ₆ H ₄ -NH-Ph	48	80
9	<i>o</i> -MeOC ₆ H ₄	<i>o</i> -MeOC ₆ H ₄ -NH-Ph	48	73
10	<i>o</i> -ClC ₆ H ₄	<i>o</i> -ClC ₆ H ₄ -NH-Ph	48	66
11 ^[b]	<i>n</i> -C ₇ H ₁₅	<i>n</i> -C ₇ H ₁₅ -NH-Ph	48	68 (62)
12 ^[b,d]	C ₆ H ₁₂ O	Cyclohexyl-NH-Ph	48	72

[a] Reaction conditions: nitrobenzene (1 mmol), alcohol (8 mmol), toluene (1 mL), and catalyst (Au/TiO₂-VS, metal: 0.5 mol %) at 120°C, under argon atmosphere. [b] Alcohol (10 mmol). [c] alcohol: 1-phenylethanol. [d] Alcohol: cyclohexanol. [e] Yields based on nitroarenes, determined by GC using *n*-dodecane as the internal standard. The numbers in parenthesis refer to yields of isolated products.

hols. Tertiary amines are important building blocks in organic synthesis and routinely served as synthons for pharmaceuticals, herbicides, agricultural chemicals, and functionalized materials.^[16] The synthesis of tertiary amines is traditionally carried out with a number of non-catalytic or catalytic procedures such as *N*-alkylation of amines with alkyl halides or alcohols,^[17] reductive amination of carbonyl compounds,^[18] or amination of alkyl halides,^[19] mostly by multi-step procedures. Despite their utility, clear drawbacks of these methods are the use of expensive amines as starting materials, low selectivity, tedious workup procedures and concomitant formation of large amounts of wasteful salts. Therefore, the development of a simple, efficient and waste-free one-pot process is of high actual interest. We have performed the straightforward one-pot reaction at 150°C using various combinations of nitroarenes and alcohols (1:8 molar ratio for all examples) with Au/TiO₂-VS. The results presented in Table 4 show that it is possible to achieve high conversion of nitroarenes with excellent selectivity to tertiary amines without the separation of aniline intermediates through this one-pot di-*N*-alkylation procedure.

The reaction profiles for the Au/TiO₂-VS-catalyzed tertiary amine formation by the direct reductive condensation of **1a** with **2a** (Figure 1)^[20] showed that the initially formed **3a'**

Table 4. Catalytic formation of tertiary amines from nitroarenes and alcohols.^[a]


Entry	R ¹	R ²	Product	Yield [%] ^[c]
1	H	C ₆ H ₅	Ph-N(C ₆ H ₅) ₂	98 (96)
2	<i>p</i> -Me	C ₆ H ₅	<i>p</i> -MePh-N(C ₆ H ₅) ₂	94
3	<i>p</i> -MeO	C ₆ H ₅	<i>p</i> -MeOPh-N(C ₆ H ₅) ₂	87
4	<i>p</i> -Cl	C ₆ H ₅	<i>p</i> -ClPh-N(C ₆ H ₅) ₂	85 (83)
5	<i>m</i> -Me	C ₆ H ₅	<i>m</i> -MePh-N(C ₆ H ₅) ₂	88
6	H	C ₆ H ₅ CH ₂	Ph-N(C ₆ H ₅ CH ₂) ₂	80
7	H	<i>p</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄ -N(C ₆ H ₅) ₂	92 (90)
8	H	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄ -N(C ₆ H ₅) ₂	81
9	H	<i>o</i> -MeC ₆ H ₄	<i>o</i> -MeC ₆ H ₄ -N(C ₆ H ₅) ₂	56
10 ^[b]	H	C ₇ H ₁₅	Ph-N(C ₇ H ₁₅) ₂	70 (67)

[a] Reaction conditions: nitroarenes (1 mmol), alcohol (8 mmol), toluene (1 mL), and catalyst (Au/TiO₂-VS, metal: 0.5 mol%) at 150°C for 48 h under argon atmosphere. [b] Catalyst (Au/TiO₂-VS, metal: 1.0 mol%). [c] Yields based on nitroarenes, determined by GC using *n*-dodecane as the internal standard. Numbers in parenthesis refer to the yields of the isolated products.

was converted to **3a** with subsequent N-alkylation to produce **3a''**. In addition, aniline and N-benzylideneaniline (**3a'**, below 10% yield) could be detected during the reaction, albeit in only small amounts. Furthermore, it was confirmed in a separate experiment that the Au-catalyzed N-alkylation of **3a** with **2a** efficiently proceeded to afford the corresponding tertiary amine **3a'** in quantitative yields (based on starting amine, see the Supporting Information).^[21] Therefore, the present reductive N-alkylation would proceed through the double (or single) N-alkylation reactions, in which alcohols act as both reducing and alkylating reagents. In the first N-alkylation, the dehydrogenation of an alcohol into the corresponding carbonyl compound initially proceeds with the transitory formation of the gold-hydride species.^[9e,12a] Then, the carbonyl compound readily reacts with anilines (produced through the reduction of **1a**) to form the corresponding imine. Finally, the hydrogen transfer reaction from the hydride species to the imine proceeds to afford the corresponding secondary amine. The second N-alkylation, if occurred,^[21] would proceed through

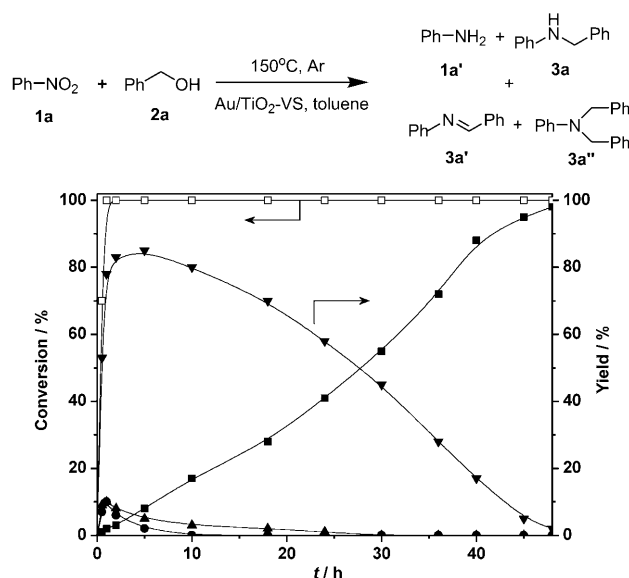


Figure 1. Reaction profile for tertiary amine synthesis from nitrobenzene and benzyl alcohol. (□) Conversion of **1a**; (●) yield of **1a'**; (▼) yield of **3a**; (▲) yield of **3a'**; (■) yield of **3a''**. Reaction conditions: nitrobenzene (1 mmol), benzyl alcohol (8 mmol), toluene (1 mL), and catalyst (Au/TiO₂-VS, metal: 0.5 mol%) at 150°C for 48 h under argon (Ar) atmosphere.

the similar sequential processes (see Figure S3 in Supporting Information) in a cascade mode, that is, 1) the dehydrogenation of an alcohol, 2) the formation of an imine (or an iminium cation), and 3) the reduction of the imine (or an iminium cation) intermediate.^[4d,5d]

In conclusion, we have reported here the noteworthy features of an Au/TiO₂-VS catalyst for the direct reductive mono- or di-N-alkylation of a range of aromatic nitro compounds with alcohols via a hydrogen-borrowing strategy. This process has significant advantages when compared with other N-alkylation methods, such as 1) cheap and readily available reactants (nitroarenes and alcohols), 2) high catalytic activity and selectivity, 3) no external molecular hydrogen or other stoichiometric reducing agents are necessary in our catalytic system, and 4) the reaction takes place without any stabilizing ligands and/or co-catalysts. We believe that the reaction chemistry described here may enable the development of new sustainable processes for clean and efficient synthesis of secondary or tertiary amines from nitroarenes with alcohols.

Experimental Section

General procedure: Nitroarene, alcohol (8 equiv), metal catalyst (0.5 mol% metal), toluene (1 mL) and *n*-dodecane (10 μL, as the internal standard) were placed into a Teflon-lined autoclave (4 mL capacity). The resulting mixture was vigorously stirred at the given temperature under an argon atmosphere (1 atm) for the given reaction time. The product was identified by GC-MS and the spectra obtained were compared with the standard spectra. The conversion and product selectivity were determined by a GC-17A gas chromatograph equipped with a HP-Free Fatty

Acid Analyses (HP-FFAP) column (30 m × 0.25 mm) and a flame ionization detector (FID). For isolation, the combined organic layer was dried over anhydrous Na₂SO₄, concentrated, and purified by silica gel column chromatography.

Recovery and reuse of Au/TiO₂-VS: The reused catalyst was recovered by filtering the solid Au/TiO₂-VS from the liquid phase after reaction. The recovered catalyst was washed with acetone three times and then washed several times with distilled water. After that, the catalyst was dried at 80 °C overnight before the next recycle run.

Acknowledgements

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Keywords: alcohols • alkylation • gold • heterogeneous catalysis • nitroarenes • one-pot reaction

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- [20] For time-dependent conversion of benzyl alcohol as well as the evolution of corresponding dehydrogenative byproducts including benzaldehyde and benzyl benzoate, see Figure S2 in the Supporting Information.
- [21] The N-alkylation of **3a** with **2a** to afford the corresponding tertiary amine proceeds smoothly at 150°C. In contrast, the same reaction practically does not occur at 120°C. See the Supporting Information for details.

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