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Direct Catalytic N-Alkylation of Amines with Carboxylic Acids

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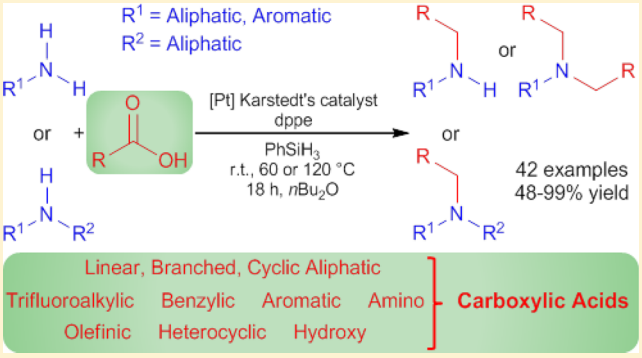
Supporting Information

ABSTRACT: A straightforward process for the N-alkylation of amines has been developed applying readily available carboxylic acids and silanes as the hydride source. Complementary to known reductive aminations, effective C−N bond construction proceeds under mild conditions and allows obtaining a broad range of alkylated secondary and tertiary amines, including fluoroalkyl-substituted anilines as well as the bioactive compound Cinacalcet HCl.

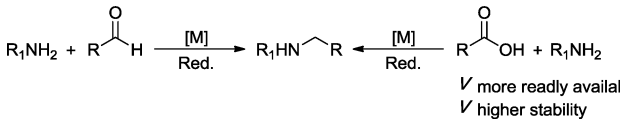


INTRODUCTION

Substituted amines play an important role in chemistry and biology. They are widely used as versatile building blocks for organic synthesis, biological systems, material science, agrochemicals, and pharmaceuticals.[1] Due to their importance, several methods for the preparation of N-alkylated aliphatic or aromatic amines have been developed.[2,3] In this respect, reductions of imines or amides represent fundamental methodologies for their preparation.[4−8] However, a drawback of these protocols is the need of additional reaction steps for the synthesis and isolation of the corresponding substrates.

In general, domino or tandem processes might allow for a more benign and straightforward route for the preparation of N-alkylated amines.[9] Among the known reaction sequences, the direct reductive amination of carbonyl compounds represents a well-established and practical approach.[4b,10,11] Here, typically aldehydes or ketones are reacted with amines in the presence of a reducing agent to afford the corresponding higher alkylated amines (Scheme 1, left side). Instead of using sensitive aldehydes, based on the previous reports on the methylation of amines applying formic acid in liquid solution[12] or generated in situ from CO_2,[13] we thought it should be possible to employ more readily available and stable carboxylic acids (Scheme 1, right side). In spite of the tremendous progress in the field of redox catalysis over the last decades, to the best of our knowledge there is only one known example on the reductive alkylation of amines with higher carboxylic acids (RCO_2H; R ≠ H). More specifically, Cole-Hamilton and co-workers reported the hydrogenation of nonanoic acid in the presence of ammonia affording a mixture of the corresponding primary and secondary amines in low yield and selectivity.[14] In contrast, the use of carboxylic acids to alkylate amines has been more extensively disclosed employing stoichiometric amounts of borohydrides.[15,16] However, the limited substrate scope and the low functional group tolerance of these reactions offer room for improvement. In this respect, herein we describe the first general and straightforward catalytic N-alkylation of primary and secondary amines using different carboxylic acids and silanes under mild reaction conditions.

Scheme 1. Conventional Reductive Amination from Aldehydes (left) Compared to N-Alkylation with Carboxylic Acids Presented in This Work (right)



RESULTS AND DISCUSSION

Based on our experience on methylation of amines[12,13b,d] as well as the few known reports on platinum-catalyzed hydrosilylation of carbonyl compounds,[17] we started to investigate the reaction of aniline (**1a**) and acetic acid in the presence of hydrosilanes. As catalysts for this benchmark reaction, in situ formed platinum complexes were tested. To our delight, applying different ligands in combination with 0.5 mol % of the commercially available Karstedt catalyst ($[Pt(CH_2{=}CHSiMe_2)_2O]$) and using phenylsilane as reducing agent the desired *N*-ethylaniline (**2a**) was formed as main product (Table 1). In addition, small amounts of the double alkylated amine, *N*,*N*-diethylaniline (**3a**), and *N*-phenylacetamide (**4a**) were obtained. Interestingly, by using 1,2-bis(diphenylphosphino)ethane (dppe; **5f**) as a ligand a slightly higher selectivity for the monoalkylation was achieved, and **2a** was afforded in 81% yield (Table 1, entry 7). Notably, the

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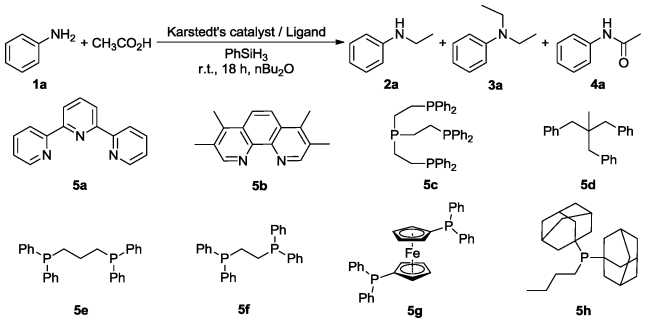
Table 1. Platinum-Catalyzed N-Alkylation of Aniline with Acetic Acid and Phenylsilane[a]



			yield (%)[b]		
entry	ligand	conversion (%)[b]	**2a**	**3a**	**4a**
1[c]	–	95	51	18	–
2	**5a**	92	74	6	–
3	**5b**	86	74	6	–
4	**5c**	49	5	–	40
5	**5d**	93	79	4	6
6	**5e**	88	67	2	11
7	**5f**	93	81	3	4
8	**5g**	88	70	2	4
9[d]	**5h**	95	82	4	–
10[d,e]	**5f**	20	–	–	20
11[e]	**5f**	>99	90	6	–
12[e,f]	**5f**	76	54	1	20
13[g]	**5f**	>99	–	>99	–

[a]Reaction conditions: **1a** (0.5 mmol), CH_3CO_2H (2 equiv), $PhSiH_3$ (3 equiv), catalyst (0.5 mol %), ligand (0.5 mol %), nBu_2O (1 mL). [b]Determined by GC using *n*-hexadecane as an internal standard. [c]$PhSiH_3$ (3.3 equiv). [d]Ligand (1 mol %). [e]CH_3CO_2H (2.2 equiv), $PhSiH_3$ (4 equiv). [f]Catalyst (0.1 mol %), ligand (0,1 mol %). [g]CH_3CO_2H (4.5 equiv), $PhSiH_3$ (8 equiv), catalyst (1 mol %), ligand (1 mol %).

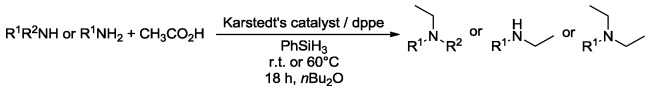
ligand-free system gave lower selectivity because of over-alkylation occurred, whereas in the presence of an excess of ligand (Pt/dppe ratio =1:2) no reactivity to the N-alkylated products was observed (Table 1, entries 1 and 10, respectively).

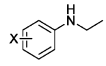
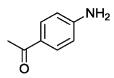
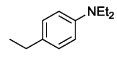
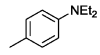
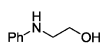
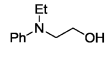
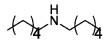
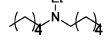
Next, other platinum sources were examined in combination with dppe (**5f**) as ligand but resulted in lower yields of the monoalkylated product **2a** (Table SI1 in the Supporting Information). In the absence of any platinum catalyst, only *N*-phenylacetamide (**4a**) was formed in 26% yield. As shown in Table SI2 (Supporting Information), no reaction or a decrease on conversion and yield took place by using other hydrosilanes, even those having dual proximate Si–H moieties in the molecule, which have been established as powerful reducing reagents for the platinum-catalyzed reduction of carboxamides to amines.[17g,h,18]

Next, an improvement of the conversion and product yield was attempted by changing the solvent. However, whereas the use of nBu_2O, Et_2O, toluene, or 1,4-dioxane had no significant influence, THF led to much lower reactivity (Table SI3 in the Supporting Information). Gratefully, by adjusting the amount of acetic acid and phenylsilane to 2.2 and 4 equiv, respectively, full conversion of aniline (**1a**) was achieved affording *N*-ethylaniline (**2a**) in 90% yield (Table 1, entry 11; see also Supporting Information, Table SI4). Reduction of catalyst loading to 0.1 mol % under otherwise identical reaction conditions led to lower conversion and yield of 54% for **2a** (Table 1, entry 12). Finally, by increasing the amount of acetic acid, silane, and catalyst loading, *N*,*N*-diethylaniline (**3a**) was afforded in near quantitative yield (99%; Table 1, entry 13).

After investigating the model reaction, the scope of this novel catalytic protocol for the alkylation of amines with acetic acid was studied in detail. As shown in Table 2, a variety of primary and secondary amines were smoothly alkylated at room temperature or 60 °C affording the corresponding N-alkylated secondary or tertiary amines with good to excellent yields.

Table 2. N-Alkylation of Amines with Acetic Acid[a]



entry	substrate	T (°C)	product	conv. (%)[b]	yield (%)[b]
					
1	X = 4-Me	r.t.	X = 4-Me	98	86
2	X = 4-Cl	r.t.	X = 4-Cl	>99	97
3[c]	X = 4-OMe	60	X = 4-OMe	96	90
4	X = 2-F	r.t.	X = 2-F	>99	91
5[d,e]		60		>99	(62)
6[d,e]		60		>99	97 (91)
7		r.t.		>99	>99 (94)
8[d]		60		>99	84
9[e,f]	$BnNH_2$	60	$BnNEt_2$	>99	79
10[d]	Bn_2NH	60	Bn_2NEt	>99	99
11[d]		60		92	88
12		60		>99	(79)

[a]Reaction conditions: substrate (0.5 mmol), CH_3CO_2H (2.2 equiv), $PhSiH_3$ (4 equiv), catalyst (0.5 mol %; M/L ratio 1:1), nBu_2O (1 mL). [b]Determined by GC using *n*-hexadecane as an internal standard; yield of isolated product in parentheses. [c]CH_3CO_2H (1.8 equiv), $PhSiH_3$ (3.3 equiv). [d]CH_3CO_2H (4.5 equiv), $PhSiH_3$ (8 equiv). [e]Catalyst (1 mol %; M/L ratio 1:1). [f]CH_3CO_2H (5.5 equiv), $PhSiH_3$ (10 equiv).

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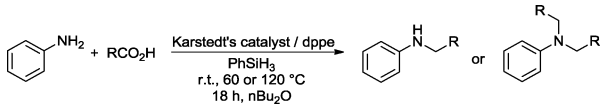
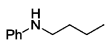
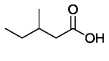
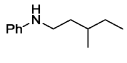
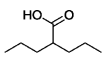
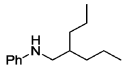
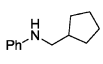
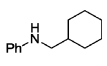
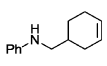
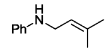
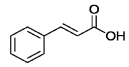
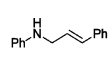
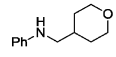
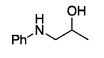
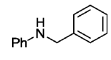
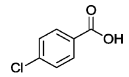
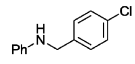
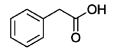
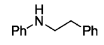
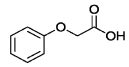
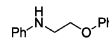
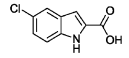
Table 3. N-Alkylation of Aniline with Various Carboxylic Acids[a]



entry	RCO_2H	T (°C)	Product	conv (%)[b]	yield (%)[b]
1		60		>99	90
2[c,d]		60		>99	95
3		60		>99	91
4		r.t.		96	90
5		60		97	(87)
6[e]		60		>99	(91)
7[f]		60		>99	(92)
8[e,g]		120		>99	(94)
9[f]		60		>99[h]	(91)
10[f]		60		94	93
11[f]		60		93	(89)
12[e]		r.t.		93	(85)
13[i]		r.t.		97	(91)
14[j]		60		93	(85)
15[f,k]		60		94	(82)
16[i]		r.t.		>99	94
17[i]		60		>99	81
18[f]		60		98	87
19		60		98	84 (75)
20[e]		60		95	(81)
21[f]		60		93	(79)
22[f]		60		78	(48)

[a]Reaction conditions: substrate (0.5 mmol), RCO_2H (2.2 equiv), $PhSiH_3$ (4 equiv), catalyst (0.5 mol %; M/L ratio 1:1), nBu_2O (1 mL). [b]Determined by GC using *n*-hexadecane as an internal standard; yield of isolated product in parentheses. [c]RCO_2H (5 equiv), $PhSiH_3$ (9 equiv). [d]Catalyst (1 mol %; M/L ratio 1:1). [e]RCO_2H (4.5 equiv), $PhSiH_3$ (8 equiv). [f]RCO_2H (2.5 equiv), $PhSiH_3$ (4.5 equiv). [g]120 °C. [h]Dodecane used as an internal standard. [i]RCO_2H (4 equiv), $PhSiH_3$ (6.5 equiv). [j]RCO_2H (3 equiv), $PhSiH_3$ (5.5 equiv). [k]THF used as a solvent.

Both, electron-donating and electron-withdrawing substituents on the aromatic ring had no significant influence on the efficiency of this methodology (Table 2, entries 1−5). In fact, the moderate yield obtained starting from 4-aminoacetophenone was due to the formation of a vinyl group after reduction of the ketone more than to a lack of alkylation (Table 2, entry 5; see also the extension of Table 2 in the Supporting Information). In addition, benzyl amines, linear as well as cyclic aliphatic amines, were also suitable for alkylation affording the corresponding N-alkylated products in up to 99% yield, although in general a higher amount of acetic acid and phenylsilane was required (Table 2, entries 9−12). Interstingly, the degree of alkylation (mono- over dialkylation) in the reaction of anilines with acetic acid can be controlled by tuning the stoichiometry of the reagents and the reaction conditions (Table 1, entry 11 vs 13, and Table 2, entry 1 vs 6). Unfortunately, this selectivity was not retained when benzylamine was used as substrate (Table 2, entry 9).

To our delight, the selective alkylation of amino alcohols without additional protection/deprotection steps was possible with this protocol (Table 2, entry 8).

Next, we focused on the alkylation of amines with more challenging carboxylic acids (Table 3). First, the reaction of anilines with acids of longer alkyl chain length was investigated (Table 3, entries 1−10). To our delight, N-alkylated anilines furnished with linear, branched, and even cyclic aliphatic moieties were afforded in 87−95% yield. Remarkably, also with propanoic acid a high control on the degree of alkylation was achieved (Table 3, entry 1 vs 2). At higher temperature (120 °C) the electron-rich *N*-neopentylaniline, whose catalytic preparation remains elusive up to now in the homogeneous version, was also accessible in excellent yield (Table 3, entry 8). When cyclohex-3-enecarboxylic acid was used as an alkylating reagent, the interior olefin was completely retained (Table 3, entry 11). Allylic carboxylic acids and the conjugated trans double bond of the cinnamic acid were also well tolerated, and the secondary N-alkylated amines were obtained in good yields with only traces (<5%) of products with reduced C−C double bond (Table 3, entries 12−13). In addition, the alkylation reaction of aniline with heterocyclic and hydroxyl-substituted carboxylic acids also gave the desired amines in 85 and 82% isolated yield, respectively (Table 3, entries 14−15). Interestingly, aromatic, benzylic as well as carboxylic acids bearing aromatic ethers could also be applied in this coupling reaction furnishing the expected products in high yields (Table 3, entries 16−19). Moreover, diamine compounds were easily accessible

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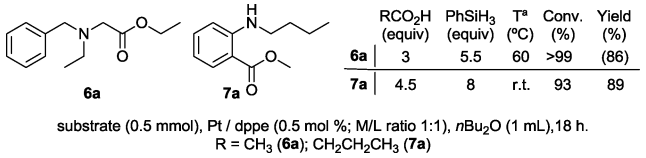
by reaction of aniline with amino carboxylic acids (Table 3, entries 20−22). Notably, the Boc- and Cbz-protecting groups (Boc = *t*-butyl carbamate; Cbz = benzyl carbamate) were well tolerated in this process, and the corresponding products were obtained in 79 and 48% isolated yields, respectively. In all cases, double bonds present in the substrates were unreactive, which makes this methodology complementary to traditional reductive aminations.

Since it is possible to alkylate amines with carboxylic esters,[16] we decided to use them instead of carboxylic acids. However, after reacting aniline with methyl benzoate under otherwise identical reaction conditions used for benzoic acid, both were recovered almost untouched (Scheme SI2 in the Supporting Information). With this uncommon reactivity in hand, we were encouraged to alkylate amines bearing esters functional groups under our protocol with carboxylic acids. To our delight, this functional moiety was well tolerated, and the corresponding alkylated amines were achieved in high yields (Scheme 2).

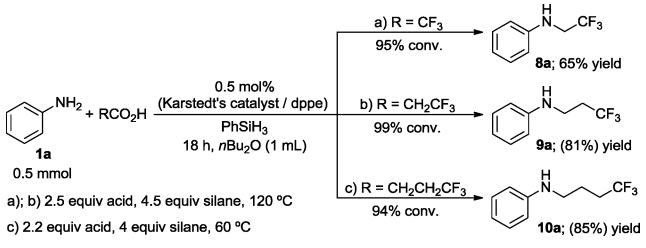
Scheme 2. N-Alkylations of Amines Bearing Esters Functional Groups[a]



[a]Yield of isolated products in parentheses.

After the successful alkylation of amines with different types of carboxylic acids, we were further interested in the application of our novel catalytic protocol for the synthesis of fluoroalkyl-substituted anilines, which are highly desired in the pharmaceutical industry.[19] Gratifyingly, reactions were successfully accomplished in moderate to good yields by applying easily available trifluoroalkylated carboxylic acids of different chain length (Scheme 3).

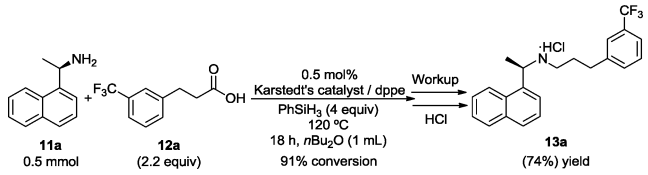
Scheme 3. Trifluoroalkylation of Aniline[a]



[a]Yield of isolated products in parentheses.

Furthermore, we demonstrated the synthetic utility of the methodology in the synthesis of Cinacalcet hydrochloride (**13a**) (e.g., AMG 073, Sensipar, Mimpara), a selective calcimimetric agent clinically used for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and hypocalcaemia in patients with parathyroid carcinoma (Scheme 4).[20] To our delight, reaction of the enantioenriched (1*R*)-(+)-1-naphthylethylamine (**11a**; ee = 88%) and 3-(3-trifluoromethylphenyl)-propionic acid (**12a**) with phenylsilane in the presence of the in situ formed platinum catalyst afforded after workup **13a** in 74% isolated yield without racemization. To the best of our knowledge, among the

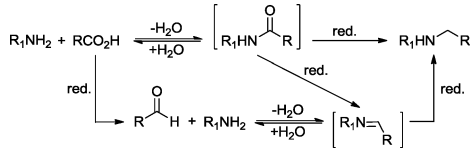
Scheme 4. One-Pot Catalytic Synthesis of Cinacalcet HCl (11a)



synthetic methodologies developed for the synthesis of this bioactive compound, our Pt-catalyzed N-alkylation procedure represents the first real one-pot catalytic sequence.[21]

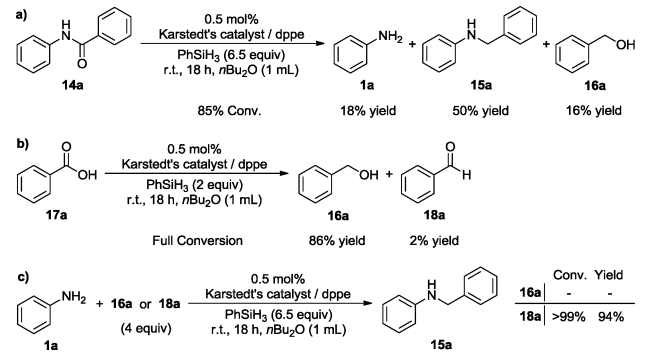
With respect to the reaction mechanism, two main pathways can be proposed for the alkylation of amines with carboxylic acids (Scheme 5): (1) direct condensation reaction to produce

Scheme 5. Proposed Pathways for the Pt-Catalyzed Alkylation of Amines with Carboxylic Acids



the carboxamides intermediates,[22] followed by in situ reduction, and (2) a conventional reductive amination of aldehydes initially generated by reduction of the corresponding carboxylic acids.[23,24] Since carboxamide intermediates were successfully detected during the investigation of the benchmark system (Table 1) and the substrate scope, the first route can be proposed as a robust mechanism. Indeed, the reduction of *N*-phenylbenzamide (**14a**) with phenylsilane (6.5 equiv) afforded benzylaniline (**15a**) in 50% yield without further optimization of reaction conditions (Scheme 6a). On other hand, to gain

Scheme 6. Control Experiments: Reduction of (a) *N*-Phenylbenzamide (14a) and (b) Benzoic Acid (17a) and (c) Reductive Amination of Benzaldehyde (18a) and Benzyl Alcohol (16a)



further insight about the feasibility of the second route, we performed some control experiments (Scheme 6b,c). Reduction of benzoic acid (**17a**) with phenylsilane mainly led to benzylalcohol (**16a**), which means that benzaldehyde (**18a**) is present in the reaction mixture as a transient species. Interestingly, when aniline (**1a**) was reacted with **18a** under otherwise identical reaction conditions used for its analogue carboxylic acid **17a**, benzylaniline (**15a**) was obtained in 94% yield. Based on these results, we conclude that both reaction

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pathways are feasible in the alkylation of amines with carboxylic acids under the present reaction conditions.

SUMMARY

We have developed a convenient and straightforward catalytic domino reaction for the N-alkylation of amines based on the use of readily available carboxylic acids and silanes as reducing agents. By applying an in situ combination of the commercially available Karstedt's catalyst and dppe as ligand, the C−N bond formation proceeds easily under mild reaction conditions to give a broad range of alkylated secondary or tertiary amines in good to excellent yields. Furthermore, the synthetic utility of this novel protocol is demonstrated in the preparation of valuable fluoroalkyl-substituted anilines and the first one-pot catalytic synthesis of Cinacalcet hydrochloride.

EXPERIMENTAL SECTION

The General Procedure for the Alkylation Reaction of Aniline with Acetic Acid. In a Schlenk tube under argon atmosphere, dppe (1 mg, 0.0025 mmol) was dissolved in dry nBu$_2$O (1 mL), and Karstedt catalyst (29 μL, 0.0025 mmol) was added leading to the formation of a slightly yellow solution. After stirring the mixture during 10 min, $PhSiH_3$ (247 μL, 2.0 mmol) was added, and the solution turned colorless. Immediately, aniline (45.6 μL, 0.5 mmol), n-hexadecane (50 μL) as an internal standard, and CH_3CO_2H (63 μL, 1.1 mmol) were added, and the reaction mixture was stirred at room temperature for 18 h. After completion, the mixture was diluted with ethyl acetate (15 mL), carefully quenched with aqueous NaOH (3 M solution; 5 mL), and stirred for 3 h at room temperature. Then, a sample was taken to be injected in the GC in order to determinate the yield. All catalytic reactions were performed at least twice to ensure reproducibility. To determine the isolated yield of the alkylated amines, no internal standard was added. The resulting mixture was extracted with ethyl acetate (three times), and the combined organic layers were dried over $MgSO_4$ anhydrous. Finally, the organic phase was filtered, concentrated, and purified by silica gel column chromatography (n-hexane/ethyl acetate mixtures) to give the corresponding alkylated amines.

Synthesis of Cinacalcet Hydrochloride (11a). The general procedure described above for the alkylation of amines with carboxylic acids was applied with minor modifications. After concentrating the organic layers under reduced pressure, the mixture was diluted with ethyl acetate (15 mL), filtered, concentrated again, and purified by silica gel column chromatography (n-heptane/ethyl acetate mixtures, from 99:1 to 80:20). Then, the resulting product was diluted with Et_2O (10 mL) and the desired hydrochloride salt of the amine was formed by addition of a HCl solution (2 M in diethyl ether; 1 mL). After overnight at −20 °C, the resulting white solid was washed with fresh Et_2O to gain Cinacalcet hydrochloride as a pure product. Yield: 74%.

ASSOCIATED CONTENT

Supporting Information

Extended data about optimization of reaction conditions and N-alkylation with acetic acid (Table 2), N-alkylation with carboxylic esters, synthesis and spectroscopic data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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