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Site-selective Linear Alkylation of Anilides by Cooperative Nickel/Aluminum Catalysis

Shogo Okumura, Takuya Komine, Erika Shigeki, Kazuhiko Semba, Yoshiaki Nakao*

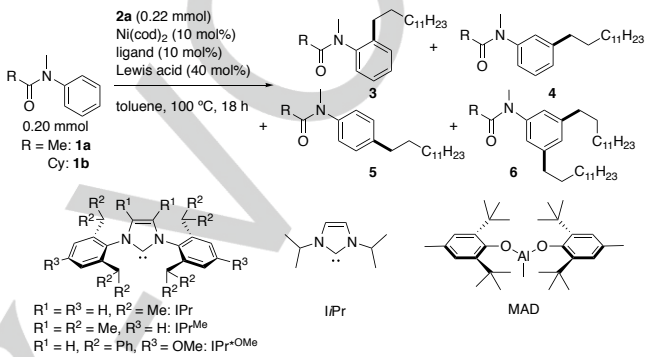
Dedication ((optional))

Abstract: We report *meta*- and *para*-selective linear alkylation of anilides with alkenes by nickel/*N*-heterocyclic carbene (NHC) and aluminum catalysis. With a relatively less bulky NHC, the alkylation reaction of *N*-methyl-*N*-phenylcyclohexanecarboxamide proceeds mainly at the *meta*-position. In contrast, a bulky NHC ligand results in the *para*-selective alkylation of *N*-(*sec*-alkyl)-anilides.

The site-selective C–H functionalization of readily available mono-substituted benzenes is one of the most effective strategies to synthesize a wide variety of poly-substituted benzenes.[1] Aniline and its derivatives are important substrates for C–H functionalizations owing to their availability and the applications of substituted anilines in pharmaceuticals, agrochemicals, and advanced materials. The C–H alkylation of anilines with alkenes as alkylating agents represents an ideal alkylation reaction in terms of atom economy. However, the *ortho*/*meta*/*para* selectivity, as well as the linear/branched selectivity remain difficult to be controlled precisely. The Friedel-Crafts alkylation of aniline with olefins proceeds selectively at the *ortho*[2] or *para*[3] positions to afford branched alkylanilines. Recently Ackermann has reported the ruthenium-catalyzed *meta*-selective tertiary alkylation of *N*-protected anilines with tertiary alkyl bromides,[4] whereas examples of the *meta*-selective branch alkylation using alkenes have not yet been reported. In contrast to the advances in branched alkylation reactions, linear alkylation reactions of aniline derivatives remain undeveloped. Although a few examples of *ortho*-selective linear alkylation of anilines bearing directing groups[5] and several methods for the direct *meta*-selective C–H functionalization of aniline derivatives have been developed,[6] *meta*- or *para*-selective linear alkylations of aniline derivatives with alkenes have not been reported so far.

Herein we report the *meta*- and *para*-selective linear alkylation of anilides using a nickel/aluminum cooperative catalysis system. We have previously reported the *para*-selective linear alkylation of benzamides and aromatic ketones by nickel/aluminum cooperative catalysis. [7] As discussed in the previous work, the *para*-selectivity was controlled by both electronic and steric factors and bulky ligands for nickel, while sterically unhindered and electron-poor C–H bonds worked best in the reaction. Therefore, we expected that, should the steric factors be neglected, the alkylation of anilides might proceed at the *meta*-position, as the *meta*-position of anilides should be less electron-rich than the *ortho*- and *para*-position on account of the resonance effect of the *N*-acylamino groups. In order to accomplish a proof-of principle for such a *meta*-selective alkylation of anilides, we chose an NHC ligand whose $\%V_{bur}$ value[8] is probably smaller than the one we used in the previous work (**L1** in Table 3).[9] The reaction of *N*-methylacetoanilide (**1a**) with 1-tridecene (**2a**) in the presence of $Ni(cod)_2$, IPr^{Me}, and MAD in toluene at 100 °C for 18 h afforded a mixture of *ortho*- (**3a**), *meta*- (**4a**), and *para*-alkylation (**5a**) products in 46% yield overall with a 21:66:13 selectivity (entry 1, Table 1) and a small amount of dialkylation products. The replacement of the acetyl group in **1a** with a cyclohexanecarbonyl group hampered the reaction at the *ortho*-position and enhanced the site-selectivity to *o*/*m*/*p* = 4:82:14, in which *m*,*m*'-dialkylation product **6b** (5% yield) was also considered (entry 2). The use of 100 mol% of MAD slightly increased site-selectivity (entry 3). The bulkier NHC ligand IPr^{*OMe} generated the products in lower yield and site-selectivity (entry 4). The less bulky ligands IPr and I*i*Pr were not effective in this reaction (entries 5 and 6) probably because it might stabilized (NHC)Ni(alkene)$_2$ complex, which seemed to be a resting state in the catalytic reaction,[10a] or slowed down the reductive elimination step. $AlMe_3$ resulted in low yields, under retention of the *meta*-selectivity (entry 7). Without Lewis acid co-catalysts, no alkylation products were obtained (entry 8).

Table 1. Conditions for the *meta*-Selective Alkylation of Anilides with 1-Tridecene.



entry	1	ligand	Lewis acid	yield of **3** + **4** + **5** (%)[a]	**3**/(**4** + **6**)/**5**[a]
1	**1a**	IPr^{Me}	MAD	46[b]	21:66:13
2	**1b**	IPr^{Me}	MAD	48 (5)[c]	4:82:14
3[d]	**1b**	IPr^{Me}	MAD	48 (8)[c]	3:84:13
4	**1b**	IPr^{*OMe}	MAD	26	<1:72:28
5	**1b**	IPr	MAD	13	8:73:19
6	**1b**	I*i*Pr•HBF_4[e]	MAD	<1	n.d.
7	**1b**	IPr^{Me}	$AlMe_3$	5	10:75:15
8	**1b**	IPr^{Me}	none	<1	n.d.

[a] Determined by GC analysis using *n*-dodecane as an internal standard and not corrected for response factors of minor isomers. [b] Dialkylation products were observed, which were not considered when determining site-selectivity. [c] Yield of **6.** Other dialkylation products were observed in GC analysis in ~1% yield, which were not considered when determining site-selectivity. [d] With 100 mol% MAD. [e] With 10 mol% NaO*t*Bu.

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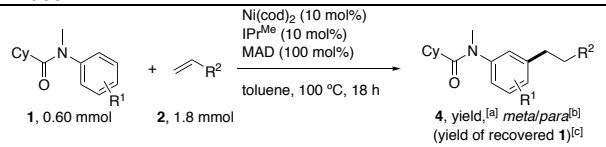
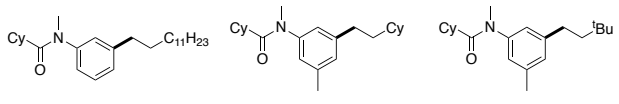
Table 2. Substrate Scope for the *meta*-Selective Alkylation of Anilides.



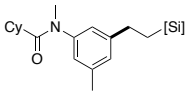
1, 0.60 mmol **2**, 1.8 mmol **4**, yield,[a] *meta*/*para*[b] (yield of recovered **1**)[c]



4b, 57% + *m,m'*-dialkylation 26%[d] *o*/(*m* + *m,m'*)/*p* = 3:83:14 (4%)

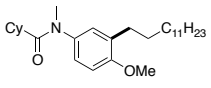
4c,[e] 45%, 95:5[f] (33%)

4d, 43%, 94:6 (42%)



[Si] = $SiMe(OSiMe_3)_2$

4e, 26%, 90:10 (64%)



4f, 67%, *m*/*o* = 95:5[f] (9%)

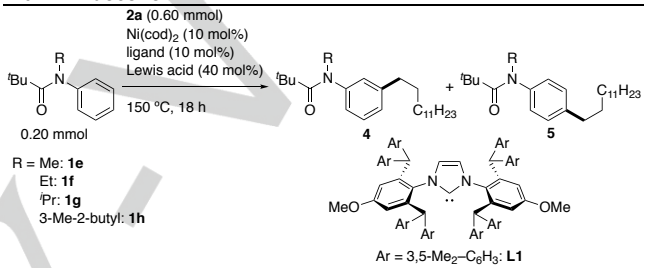
[a] Isolated yield of the mixture of **4** and its isomers. [b] Determined by GC analysis. [c] Isolated yields. [d] Containing other dialkylation products (~3% based on **1**), which were not considered when determining site-selectivity. [e] With 3.0 mmol of vinylcyclohexane. [f] Determined by ^{1}H NMR analysis of crude products.

Subsequently, we investigated the substrate scope of the alkylation. *N*-Methyl-*N*-(3-methylphenyl)cyclohexanecarboxamide (**1c**) was reacted with several alkenes. 1-Alkenes bearing cyclohexyl (**2b**) or *tert*-butyl (**2c**) groups furnished *meta*-alkylation products **4c** and **4d**, respectively, in moderate yield with high site-selectivities. The use of bulky vinylsilane (**2d**) resulted in a decreased yield of anilide **4e**. 1,1-Disubstituted alkenes gave the alkylation products in <10% yields (See Supporting Information). 2-Octene and cyclohexene did not participate in the *meta*-alkylation reaction at all under these conditions. Methoxy group at the *para*-position of **1b** did not affect the *meta*-selectivity to give **4f**. Unfortunately, *o*-acetyl and *o*-dimethylamino groups did not tolerate under the reaction conditions (see Supporting Information).

We further examined the reaction conditions for the *para*-selective alkylation of anilides by using steric factors according to our previous work (*vide supra*). The reaction of **1b** with **2a** in the presence of $Ni(cod)_2$, **L1**, and MAD at 150 ºC for 18 h afforded *meta*- (**4b**) and *para*-alkylated anilides (**5b**) in 33% yield with a *m*/*p* selectivity of 51:49 (entry 1, Table 3). The replacement of the cyclohexanecarbonyl group to a pivaloyl group enhanced the yield and the *para*-selectivity (entry 2). The introduction of bulkier *N*-alkyl groups on the anilide, such as ethyl (**1f**) or *iso*-propyl (**1g**) groups, increased the site-selectivity (entries 3 and 4). Using *N*-(3-methyl-2-butyl)-*N*-pivaloyl-aniline (**1h**), the alkylation proceeded in 70% yield with a *m*/*p* selectivity of 11:89 (entry 5). No significant improvements of the yield and site-selectivity were observed with the use of 100 mol% MAD (entry 6). We then optimized the catalysis with **1h**. While less bulky ligands such as IPr, IPr^{Me}, and IPr^{*OMe} did not work well (entries 7–9), the steric demand of the Lewis-acid co-catalyst affected the site-selectivity; using $AlMe_3$ instead of MAD lowered the *para*-selectivity (78:22; entry 10). In its absence, the alkylation products were obtained in only 15% yield with a *m*/*p* selectivity of 24:76 (entry 11).

Thereafter, we investigated the substrate scope. **2b** and **2c** afforded *para*-alkylated anilides in 68% and 71% yield, respectively. Using vinylsilane **2d**, a high *para*-selectivity was observed even though the *N*-substituent on the anilide was a sterically moderately demanding *iso*-propyl group. Methylenecyclohexane (**2e**) participated in the *para*-alkylation reaction albeit in low yield. The linear alkylation product was obtained even with 2-octene (**2f**), possibly through its reversible isomerization to 1-octene under the reaction conditions.[10a] Using **2d**, the effect of a substituent at the *ortho*-position of the anilides was studied. A 2-methyl-substituted anilide participated in the alkylation reaction. Absolute C4-selectivity was observed for a 2-methoxy-substituted anilide with low conversion, while a 2-trifluoromethoxy group retarded the alkylation reaction. 2-Fluoro group did not affect the alkylation reaction whereas a 2-chloro-substituted anilide underwent no alkylation but the Heck-type reaction (see Supporting Information). The presence of a 2-methoxycarbonyl group lowered the *para*-selectivity. No alkylation reaction was observed with *para*-substituted anilides.

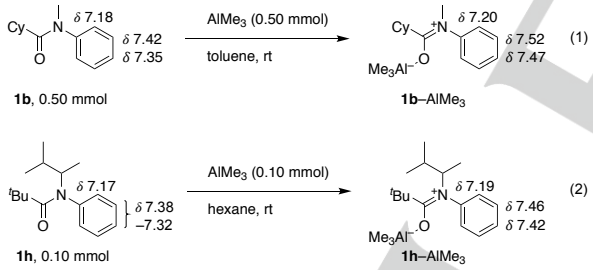
Table 3. Conditions for the *para*-Selective Alkylation of Anilides with 1-Tridecene.



entry	**1**	ligand	LA	yield of **4** + **5** (%)[a]	**4**/**5**[a]
1[b]	**1b**	**L1**	MAD	33[c]	51:49
2[b]	**1e**	**L1**	MAD	74[c]	37:63
3[b]	**1f**	**L1**	MAD	80[c]	28:72
4[b]	**1g**	**L1**	MAD	66[c]	24:76
5	**1h**	**L1**	MAD	70[d]	11:89
6[e]	**1h**	**L1**	MAD	65	10:90
7	**1h**	IPr	MAD	7	44:56
8	**1h**	IPr^{Me}	MAD	8	56:44
9	**1h**	IPr^{*OMe}	MAD	24	40:60
10	**1h**	**L1**	$AlMe_3$	48	22:78
11	**1h**	**L1**	none	15	24:76

[a] Determined by GC analysis using *n*-dodecane as an internal standard and not corrected for response factors of minor isomers. [b] 0.60 mmol scale. [c] Determined by ^{1}H NMR analysis. [d] An unidentified product, which could be an *ortho*- or branch-alkylation product was also observed by GC and GC-MS in around 1% yield estimated by GC but was difficult to characterize due to a small quantity. [e] with 100 mol% of MAD.

The electronic effect of the anilides seems to be crucial for the *meta*-selectivity. The ^{1}H NMR spectrum of a mixture of **1b** or **1h** and $AlMe_3$ revealed that the *meta*-positions of **1**-$AlMe_3$ should carry less electron density than the *para*-position, as the signal for the *meta*-H appeared at lower magnetic field (Eq. 1 and 2). As discussed in the previous report, electron-deficient positions are privileged for C–H activations *via* the LLHT[10] mechanism. Furthermore, the reductive elimination from a (*meta*-aryl)(alkyl)Ni(II) intermediate may be more favorable than that from a (*para*-aryl)(alkyl)Ni(II) species. Previous studies have also shown that the rate of the reductive elimination from (aryl)(alkyl)palladium(II) complexes to form C–C bonds depends on the electronic properties of aryl groups.[11] The reductive elimination from palladium complexes containing a more electron-rich aryl group is slower than that from complexes containing an electron-poor aryl group. Based on this knowledge, we speculate that the reductive elimination from (*meta*-aryl)(alkyl)Ni(II) intermediates could be faster than that from (*para*-aryl)(alkyl)Ni(II) intermediates, when the aryl groups are based on anilides. In contrast to the *meta*-selectivity, the *para*-selectivity of the alkylation of **1g** and **1h** by Ni/**L1** is probably governed by steric effects. The combination of bulky substituents on the nitrogen atom of the anilides (R in Table 3) and the bulky NHC ligand is essential for the *para*-selectivity (Table 3), which would suggest that the steric repulsion between the R group and NHC hampers the reaction at the *meta* position and results in *para*-selectivity. The significant enhancement of the *para*-selectivity in the presence of MAD can be explained by the steric repulsion between MAD and R, which may direct the alkyl group R to the benzene ring and inhibit the C–H bond cleavage at the *meta*-position.

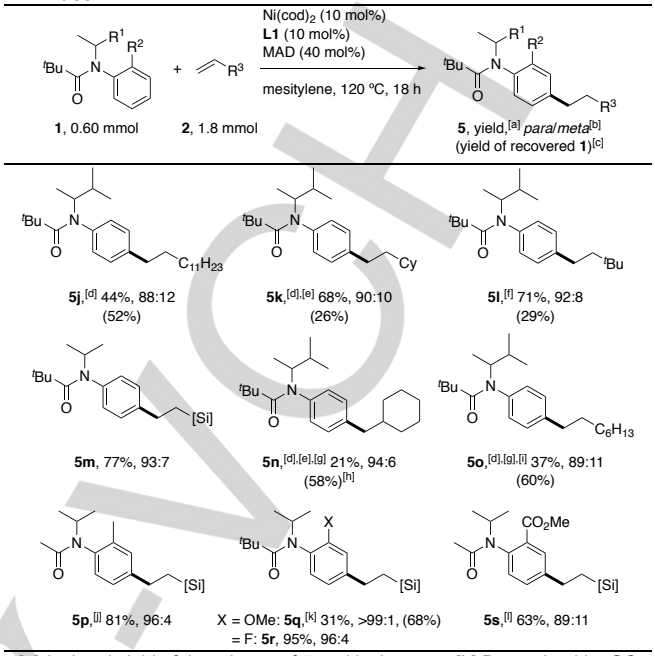


In summary, we have developed *meta*- and *para*-selective linear alkylations of anilides by cooperative nickel/aluminum catalysis. The use of IPr^{Me}, i.e., an NHC with relatively low steric demand, as a ligand for the nickel catalyst enables *meta*-selective alkylations. The bulkier NHC **L1** results in a *para*-selective alkylation of *N*-(*sec*-alkyl)-anilides. The site-selectivity is probably governed by both electronic and steric effects: the alkylation reaction may electronically favor *meta*-C–H bonds, while it should sterically favor *para*-C–H bonds, which could be the origin of the switchable site-selectivity.

Experimental Section

In a glove box, a 4-mL vial was charged with $Ni(cod)_2$ (17 mg, 60 μmol), a ligand (60 μmol), and toluene or mesitylene (0.60 mL), and the resulting mixture was stirred for 5–10 min at rt (solution A). Another 4-mL vial was charged with **1** (0.60 mmol), **2** (1.8 mmol), MAD (115 mg, 0.24 mmol or 0.29 g, 0.60 mmol), and solution A. The resulting mixture was stirred for 18 h at 100 or 150 ºC. After the mixture was cooled to rt, ethyl acetate was added to the mixture. The site-selectivity was determined by GC analysis. The mixture was filtered through a short pad of silica gel. The filtrate was purified by medium pressure liquid chromatography (MPLC) using Biotage® SNAP Ultra to give the corresponding products. For the reactions without solvents, a 4-mL vial was charged with **1** (0.60 mmol), $Ni(cod)_2$ (17 mg, 60 μmol), **L1** (70 mg, 60 μmol), MAD (115 mg, 0.24 mmol), and **2** (1.8 mmol). The resulting mixture was stirred for 18 h at 150 ºC. The same purification as above gave the corresponding products.

Table 4. Substrate Scope for the *para*-Selective Alkylation of Anilides.



[a] Isolated yield of the mixture of **5** and its isomers. [b] Determined by GC analysis. [c] Isolated yield. [d] at 150 ºC without mesitylene. [e] With 5.0 equiv of alkene. [f] In toluene instead of mesitylene. [g] 0.20 mmol scale. [h] Estimated by ^{1}H-NMR analysis of a crude product. [i] With 1.0 mmol of 2-octene. [j] 1.0 mmol scale. [k] With two portions of 1.8 mmol of **2d**. [l] With 100 mol% of MAD.

Acknowledgements

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Keywords: C–H functionalization • Cooperative catalysis • Nickel • Alkenes

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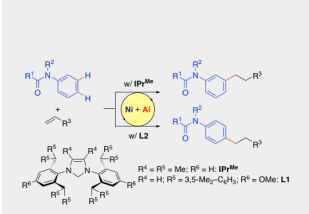

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