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Dicumyl Peroxide as a Methylating Reagent in the Ni-Catalyzed Methylation of Ortho C−H Bonds in Aromatic Amides

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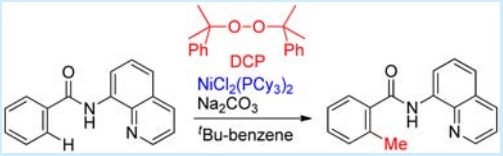
Supporting Information

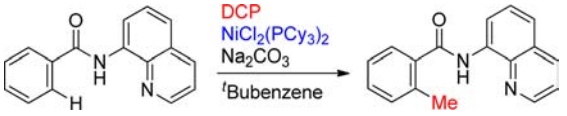
ABSTRACT: The direct methylation of ortho C−H bonds in aromatic amides with dicumyl peroxide (DCP) using a nickel complex as the catalyst is reported. The reaction shows a high functional group tolerance and is inhibited by radical scavengers. In reactions of meta-substituted aromatic amides, the reaction proceeds in a highly selective manner at the less hindered C−H bonds.



The transition-metal-catalyzed functionalization of C−H bonds is emerging as a powerful method for use in C−C bond formation and has received a great deal of attention in recent years.[1] Various C−C bond formation reactions such as arylation, alkylation, benzylation, allylation, and carbonylation with the cleavage of C−H bonds have been reported to date. However, methylation of C−H bonds continues to remain an undeveloped area[2] compared with the other types of C−C bond formation reactions. Although the methyl group is one of the simplest functional groups, the introduction of a methyl group at a C−H bond can have a significant effect on the biological and physical properties of a drug, an effect that is known as the magic methyl effect.[2a] The most extensively studied direct methylation of C−H bonds involves the use of electrophilic reagents, such as MeI and its equivalents[3] and $PhMe_3NI$.[4] Nucleophilic organometallic reagents, such as Me_4Sn,[5] methylboron reagents,[6] MeMgCl,[7] Me_3Al,[8] and Me_2Zn[9] also can be used in the oxidative methylation of C−H bonds. In addition, peroxide,[10] DMSO,[11] and other reagents[12] have also been found to function as methylating reagents.

We recently reported a series of Ni-catalyzed chelation-assisted functionalizations of C−H bonds in which a combination of a Ni(II) catalyst and an 8-aminoquinoline directing group was found to be a superior system for Ni-catalyzed chelation-assisted C−H bond activation.[3m,4,13,14] This represents the first general system for Ni-catalyzed chelation-assisted functionalization of C−H bonds. Although the precise mechanism responsible remains unclear, a radical species is thought to be involved as a key intermediate on the basis of mechanistic experiments.[3m] Peroxides such as di-*tert*-butyl peroxide (TBP) and dicumyl peroxide (DCP) are known to undergo thermal decomposition to generate a methyl radical through β-scission of an alkoxy radical, which initiates the polymerization of alkenes[15] or functions as a methylating reagent.[16] In addition, the functionalization of C−H bonds with a radical species would demonstrate the potential for a new generation of C−H bond activation reactions.[17,18] Our working hypothesis involves a reaction sequence in which an intermediate nickelacycle reacts directly with a methyl radical generated during the reaction. We herein report the Ni-catalyzed methylation of C−H bonds in aromatic amides with DCP (Scheme 1).

Scheme 1. Dicumyl Peroxide as an Ortho C−H Bond Methylating Reagent in the Ni-Catalyzed Reaction of Aromatic Amides



When amide **1** (0.3 mmol) was reacted with DCP (0.6 mmol) in the presence of a Ni(II) complex as a catalyst and Na_2CO_3 as a base in *tert*-butylbenzene at 140 °C for 18 h, the expected methylation product **2** was not produced (Table 1, entries 1−3). However, the addition of PPh_3 gave **2**, albeit in low yields (entries 4−7). To our delight, the yield was dramatically increased when PCy_3 was used as a ligand (entries 8 and 9). The efficiency of the reaction was also significantly affected by the nature of the base used, and Na_2CO_3 was found to be the base of choice (entries 9−11). The use of TBP decreased the yield of **2** (entry 12). Carrying out the reaction at 120 °C (entry 13), for a shorter reaction time (e.g., 12 h; entry 14), or with a decreased amount of DCP (entry 15) had no effect on the efficiency of the reaction. $Pd(OAc)_2$, $CoBr_2$, and $[RuCl_2(p\text{-cymene})]_2$ did not show any catalytic activity. Finally, the standard reaction conditions were determined to be as follows: **1** (0.3 mmol), DCP (0.6 mmol), $NiCl_2(PCy_3)_2$ (0.03 mmol), and Na_2CO_3 (0.9 mmol) in *tert*-butylbenzene as the solvent (0.7 mL) at a temperature of 140 °C for 18 h.

The scope of this methylation reaction with respect to the amide and functional group tolerance was explored under the standard reaction conditions (Table 2). Methoxy, benzyloxy, fluoro, chloro, bromo, ketone, trifluoromethyl, and cyano groups were tolerated under the reaction conditions. In the case

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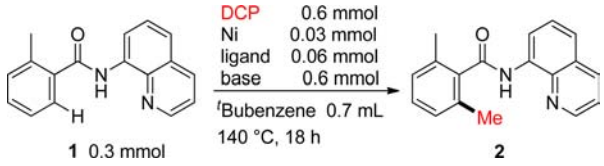
Table 1. Ni-Catalyzed Methylation of C−H Bonds with Dicumyl Peroxide



1 0.3 mmol **2**

entry	Ni catalyst	ligand	base	yields (%)[a] 2	1
1	NiI_2	-	Na_2CO_3	3	49
2	$NiCl_2$	-	Na_2CO_3	0	36
3	$NiCl_2$(glyme)	-	Na_2CO_3	trace	46
4	NiI_2	PPh_3	Na_2CO_3	26	26
5	$Ni(acac)_2$	PPh_3	Na_2CO_3	18	46
6	$Ni(OAc)_2\,4H_2O$	PPh_3	Na_2CO_3	13	47
7	$NiCl_2(PPh_3)_2$	-	Na_2CO_3	11	49
8	$NiCl_2$	PCy_3	Na_2CO_3	71	12
9	$NiCl_2(PCy_3)_2$	-	Na_2CO_3	75	2
10	$NiCl_2(PCy_3)_2$	-	K_2CO_3	53	11
11	$NiCl_2(PCy_3)_2$	-	K_3PO_4	54	0
12[b]	$NiCl_2(PCy_3)_2$	-	Na_2CO_3	28	30
13[c]	$NiCl_2(PCy_3)_2$	-	Na_2CO_3	71	6
14[d]	$NiCl_2(PCy_3)_2$	-	Na_2CO_3	74	3
15[e]	$NiCl_2(PCy_3)_2$	-	Na_2CO_3	72	15
16[f]	**$NiCl_2(PCy_3)_2$**	-	**Na_2CO_3**	**81 (78)**	**0**
17[f]	$Ni(cod)_2$	PCy_3	Na_2CO_3	36	23

[a]NMR yields. The value in parentheses is an isolated yield. [b]TBP was used. [c]Run at 120 °C. [d]Run for 12 h. [e]DCP (0.48 mmol) was used. [f]Na_2CO_3 (0.9 mmol) was used.

of meta-substituted aromatic amides, only the less hindered C−H bond was methylated.

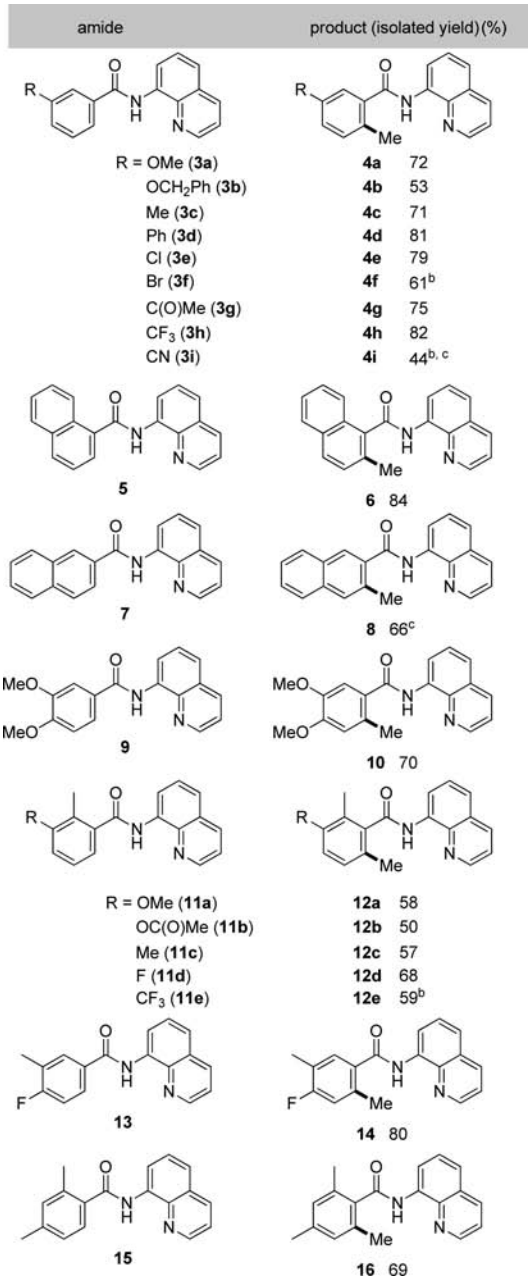
We next performed a series of experiments in order to gain insight into the mechanism. When the reactions were carried out in the presence of 3 equiv of a typical radical scavenger such as TEMPO, 1,4-cyclohexadiene, or α-methylstyrene under otherwise standard reaction conditions, the reaction was completely inhibited (Scheme 2). TEMPO methyl ether was detected by high-resolution MS when TEMPO was added.[19] These results clearly indicate that a free radical species is involved in the reaction.

A deuterium labeling experiment was also carried out with deuterium-labeled amide **1-*d*$_7$** (Scheme 3). A significant amount of H/D exchange was observed but only at the ortho C−H bond in the recovered amide **1-*d*$_7$**, indicating that C−H bond cleavage is reversible (Scheme 3a). In addition, an observed intermolecular kinetic isotope effect (KIE) of 1.15 (for parallel experiments) suggests that C−H bond cleavage is not involved in the rate-determining step (Scheme 3b).[20]

To collect additional information regarding the mechanism, we examined the effect of the electronic nature of the substituents. Similar to the case of alkylation and arylation reactions,[3m,14a,d] an electron-withdrawing group on the aromatic ring facilitated the reaction (Scheme 4).

On the basis of the results obtained in previously reported Ni(II)-catalyzed functionalization reactions[3m,14a,d] and the present observations, a mechanism involving a Ni(II)/Ni(IV) catalytic cycle is illustrated in Scheme 5. The most important issues to be addressed involve how the methyl group is generated and how it is incorporated into the product. The

Table 2. Ni-Catalyzed Methylation of C−H Bonds with Dicumyl Peroxide[a]



[a]Reaction conditions: **1** (0.3 mmol), DCP (0.6 mmol), $NiCl_2(PCy_3)_2$ (0.03 mmol), and Na_2CO_3 (0.9 mmol) in *tert*-butylbenzene (0.7 mL) at 140 °C for 18 h. [b]$NiCl_2(PCy_3)_2$ (0.045 mmol) was used. [c]Isolated by GPC.

reaction begins with coordination of amide **A** to a Ni(II) species, followed by ligand exchange and subsequent reversible cleavage of the ortho C−H bond to give nickelacycle **B**. A plausible mechanism involves a single electron transfer (SET)-type process from **B** to DCP, which gives the Ni(III) species **C** and alkoxy radical, which are in close proximity to one another. The alkoxy radical undergoes decomposition with concomitant elimination of acetophenone to give a methyl radical, which immediately reacts with the unstable Ni(III) species **C** to give the Ni(IV) species **D**. Reductive elimination followed by protonation gives the expected product **F** with regeneration of Ni(II).

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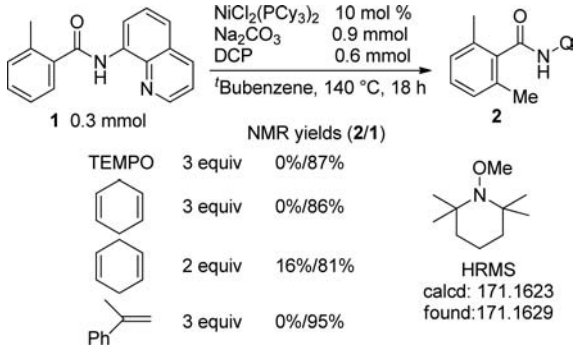
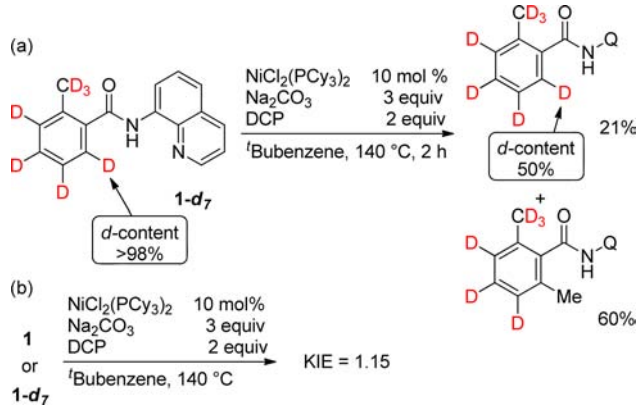
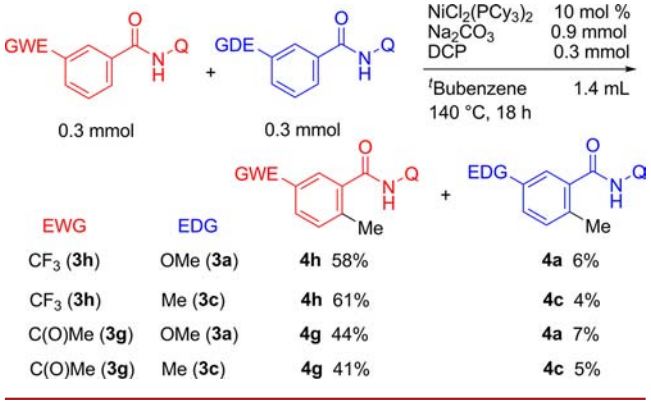
Scheme 2. Radical Trap Experiments



Scheme 3. Deuterium Labeling Experiments



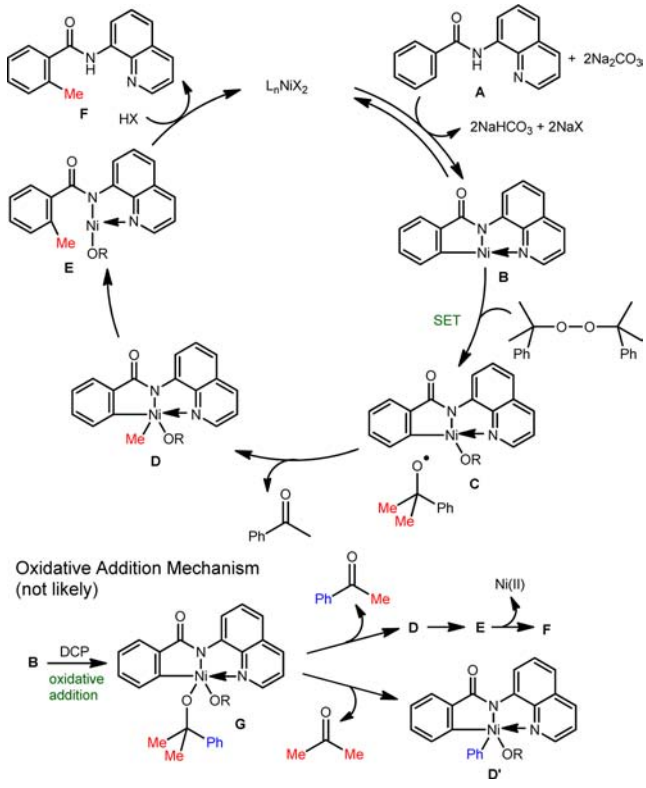
Scheme 4. Competition Experiments



An alternative mechanism involves oxidative addition of the O−O bond in DCP to the nickel center to give the Ni(IV) species **G**. Complex **G** undergoes β-methyl elimination with concomitant generation of acetophenone to give **D**. Reductive elimination from complex **D** followed by protonation gives the final product **F** with regeneration of Ni(II). However, this mechanism is inconsistent with the fact that β-phenyl elimination leading to **D′** takes place preferentially over β-methyl elimination in alkoxymetal species.[21] In addition, this mechanism is not consistent with the results of the radical trapping experiments, which indicate that a radical species is involved in the reaction.

In summary, we have reported the successful development of a highly efficient process for Ni(II)-catalyzed methylation of C−H bonds. This is the first example of the use of DCP for Ni-catalyzed methylation of C−H bonds.[10] The presence of the

Scheme 5. Proposed Mechanism



PCy_3 ligand is essential for the success of the reaction. The reaction displays a broad substrate scope and high functional group tolerance. The reaction is inhibited by radical scavengers, such as TEMPO, 1,4-cyclohexadiene, and α-methylstyrene. The results of deuterium labeling experiments and KIE experiments suggest that the C−H bond cleavage is reversible. The results of competition experiments suggest that a reductive elimination is likely to be a rate-determining step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00658.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) The possibility that the methyl TEMPO ether was produced from TEMPO and a methyl radical that was not generated in the main catalytic cycle but simply by thermal decomposition of DCP under the reaction conditions employed cannot be excluded.

(20) For details, see the Supporting Information.

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