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Nickel(0)-Catalyzed Cyclization of *N*-Benzoylaminals for Isoindolinone Synthesis

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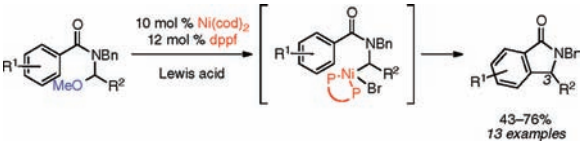
ABSTRACT



A nickel(0) catalyst effectively mediates the cyclization of *N*-benzoyl aminals in the presence of a stoichiometric Lewis acid. This method enables preparation of a variety of isoindolinones with substitution on the benzoyl fragment and C-3 carbon. This reaction likely proceeds via an α-amidoalkylnickel(II) intermediate, which then may cyclize via either an electrophilic aromatic substitution or an insertion pathway.

Efficient formation of nitrogen heterocycles from readily available starting materials is crucial for the synthesis of various pharmaceutical compounds, agrochemicals, and materials. One privileged substructure is the isoindolinone, or phthalimidine, nucleus. Isoindolinones with carbon substitution at C-3 are found in a number of biologically active molecules and natural products,[1] including the anxiolytic pagoclone[2] and naturally occurring pestalachloride A[3] (Figure 1). There are a variety of methods for building this important structure from 1,2-disubstituted benzenes, such as 1,2-diacylbenzenes, unsubstituted isoindolinones, and *o*-halobenzoic amides.[4] Isoindolinones can also be prepared via C−H functionalization of a monosubstituted benzene ring by directed ortho lithiation[5] or transition-metal-catalyzed carbonylations.[6] More recently, palladium- and rhodium-catalyzed oxidative olefinations of benzoic amides have been developed.[7] C−H functionalization has also been accomplished via triflic acid promoted aza-Nazarov cyclizations of *N*-benzoyl iminium chlorides.[8]

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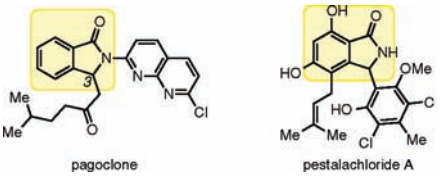
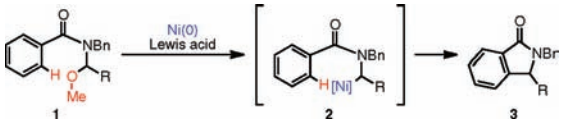


Figure 1. Examples of bioactive and natural isoindolinones.

Aminals are attractive starting materials that can be easily accessed from acid chlorides, imines, and primary amines.[9,10] However, there are few methods for using transition metal catalysts to activate aminals despite their potential to promote novel reactivity.[11] The Arndtsen group has shown that the addition of Pd catalysts to such aminals allows unique reaction pathways via catalytic formation of α-amidoalkylpalladium intermediates.[12] Very recently, Doyle has shown that Ni catalysts can be used to couple aryl boroxines with aminal substrates.[13]

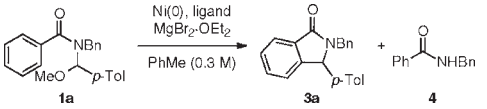
Scheme 1. Ni-Catalyzed Synthesis of Isoindolinones via Intramolecular C−H Functionalization



Herein, we describe a process for preparing isoindolinones **3** via intramolecular cyclization of *N*-benzoylaminals **1** (Scheme 1). This Ni-catalyzed process involves aromatic C−H functionalization of the benzoyl group and offers a convergent, 3-step approach for preparing isoindolinones from benzoyl chorides, primary amines, and aldehydes.

Optimization of the reaction conditions focused on cyclization of substrate **1a**, which can be readily prepared in 82% yield by benzoylation and trapping of the *N*-benzylimine of *p*-tolualdehyde.[12,14] When **1a** was heated in the presence of $NiCl_2 \cdot DME$, P(*o*-Tol)$_3$ and $AlMe_3$, isoindolinone **3a** formed in 60% yield, as was undesired amide **4** (Table 1, entry 1). To enable greater functional group tolerance, we examined a variety of milder Lewis acids. An extensive screen revealed that $MgBr_2 \cdot OEt_2$ could replace the harsher $AlMe_3$, albeit in reduced yield (entry 2). With $MgBr_2 \cdot OEt_2$, Ni(cod)$_2$ was required as the Ni source; the use of $NiCl_2 \cdot DME$ did not lead to efficient cyclization (not shown). With $MgBr_2 \cdot OEt_2$, 1,1′-bis(diphenylphosphino)ferrocene (dppf) was found to be the optimal ligand (entry 6). To minimize formation of **4** further, the reaction temperature was lowered to 95 °C (entry 7).[15] Reducing the catalyst loading led to lower yields (entry 8), and a small increase in yield was observed with higher catalyst loading (entry 9). Using the conditions shown in entry 7 (bold), **3a** was isolated in 67% yield with minimal formation of undesired **4**.

Table 1. Optimization of Isoindolinone Formation[a]



entry	Ni (mol %)	ligand (mol %)	temp (°C)	time (h)	yield (%)[b]
1[c]	$NiCl_2 \cdot DME$ (10)	P(*o*-Tol)$_3$ (22)	110	4	(60)
2	Ni(cod)$_2$ (10)	P(*o*-Tol)$_3$ (22)	110	4	31
3	Ni(cod)$_2$ (10)	$PCyPh_2$ (22)	110	4	35
4	Ni(cod)$_2$ (10)	bpy (12)	110	4	37
5	Ni(cod)$_2$ (10)	dppp (12)	110	4	36
6	Ni(cod)$_2$ (10)	dppf (12)	110	5	60
7	**Ni(cod)$_2$ (10)**	**dppf (12)**	**95**	**24**	**(67)**
8	Ni(cod)$_2$ (5)	dppf (6)	95	24	61
9	Ni(cod)$_2$ (20)	dppf (22)	95	24	74
10	Ni(cod)$_2$ (10)	BINAP (12)	95	24	56
11[c]	(0)	(0)	95	24	0
12	(0)	(0)	95	24	5
13[d]	$NiCl_2 \cdot DME$ (10)	P(*o*-Tol)$_3$ (22)	110	4	0

[a] Conditions: Substrate **1a** (0.064 mmol), [Ni], Ligand, Lewis acid (0.127 mmol, 2.2 equiv), PhMe (0.2 mL, 0.3 M). [b] Yield of **3a**, determined by NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Numbers in parentheses are isolated yields. [c] $AlMe_3$ was used instead of $MgBr_2 \cdot OEt_2$. [d] No Lewis acid used.

Both a nickel catalyst and Lewis acid are required for high yields of isoindolinone **3a**. In the absence of nickel, use of $AlMe_3$ resulted in no desired product and significant decomposition (Table 1, entry 11). $MgBr_2 \cdot OEt_2$ alone produced only trace amounts of product **3a** (entry 12). In addition, no product forms in the absence of a Lewis acid (entry 13).

As shown in Table 2, isoindolinones **3** with a variety of aryl substituents at R^2 could be prepared by this method, including that with a sterically demanding 3,5-dimethylphenyl substituent (entry 2) and those with electronically different aryl groups (entries 3−6). However, substrates with moderately electron-poor substituents required longer reaction times (entries 3, 4). The cyclization of substrates with very electron-poor groups, such as *p*-trifluoromethylphenyl, was not possible under these conditions (not shown). Further, aminals with heteroaromatic R^2 substituents, such as 2-furyl, decomposed under the optimized conditions (not shown). The use of $MgBr_2 \cdot OEt_2$ allowed preparation of *p*-bromophenylsubstituted product **3c**; with $AlMe_3$ cross-coupling of the bromide resulted in formation of product **3a** in 33%

(9) Enantioenriched aminals can also be prepared by the addition of alcohol to an imine. See: Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

(10) Aminals can also be prepared from the amide and acetal. See: Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299.

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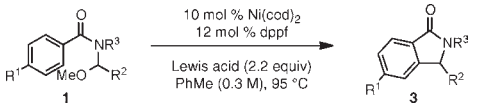
(14) See Supporting Information for full experimental details.

(15) The Arndtsen group has attributed amide formation to thermal decomposition of the iminium ion. See: Siamaki, A. R.; Arndtsen, B. A *J. Am. Chem. Soc.* **2006**, *128*, 6050.

Table 2. Scope of Cyclization[a]



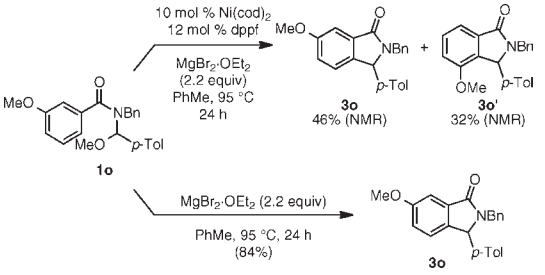
	3				
entry	R^1	R^2		Lewis acid	yield (%)[b]
1	H	*p*-Tol	**a**	$MgBr_2 \cdot OEt_2$	70
2	H	3,5-$(Me)_2C_6H_3$	**b**	$MgBr_2 \cdot OEt_2$	67[c]
3[d]	H	4-BrC_6H_4	**c**	$MgBr_2 \cdot OEt_2$	73
4[d]	H	4-FC_6H_4	**d**	$MgBr_2 \cdot OEt_2$	66
5	H	3-$(OMe)C_6H_4$	**e**	$MgBr_2 \cdot OEt_2$	76[c]
6	H	4-$(OMe)C_6H_4$	**f**	$AlMe_3$	45[c]
7	H	*t*-Bu	**g**	$MgBr_2 \cdot OEt_2$	0
8	H	*t*-Bu	**g**	$AlMe_3$	69
9	Me	*p*-Tol	**h**	$MgBr_2 \cdot OEt_2$	69
10	OMe	*p*-Tol	**i**	$MgBr_2 \cdot OEt_2$	74
11[e]	NMe_2	*p*-Tol	**j**	$MgBr_2 \cdot OEt_2$	62
12[e]	NMe_2	Ph	**k**	$MgBr_2 \cdot OEt_2$	65
13[e]	Br	*p*-Tol	**l**	$MgBr_2 \cdot OEt_2$	68
14	CF_3	*p*-Tol	**m**	$MgBr_2 \cdot OEt_2$	0
15[f]	H	*p*-Tol	**n**	$MgBr_2 \cdot OEt_2$	43

[a] Conditions: Substrate **1** (0.138 mmol), $Ni(cod)_2$ (0.014 mmol, 10 mol %), dppf (0.017 mmol, 12 mol %), $MgBr_2 \cdot OEt_2$ (0.304 mmol, 2.2 equiv), PhMe (0.5 mL, 0.3 M), 95 °C, 24 h, R^3 = Bn, unless otherwise noted. [b] Average isolated yield from duplicate experiments unless otherwise noted (±3%). [c] Yield from a single experiment. [d] Heated for 48 h. [e] Heated for 36 h. [f] R^3 = PMB.

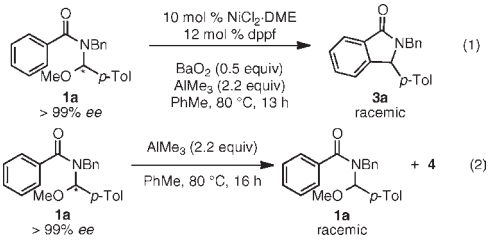
isolated yield from bromide **1c**. Although most substrates cyclized in higher yield when $MgBr_2 \cdot OEt_2$ was used instead of $AlMe_3$, aminals **1f** and **1g** did not cyclize under the standard conditions. The stronger Lewis acid, $AlMe_3$, was required for these substrates (entries 6−8). In addition, a variety of substituents (R^1) were tolerated on the benzoyl fragment, including electron-rich substituents (entries 10−12) and a bromide group (entry 13). However, substrates with electron-withdrawing groups, such as trifluoromethyl, on the benzoyl fragment failed to produce any of the corresponding isoindolinone (entry 14). Heteroaromatic aminals, such as that derived from pyrazinecarboxylic acid, also failed to cyclize under the optimized reaction conditions and instead decomposed (not shown). Finally, *p*-methoxybenzyl can be used as an alternative nitrogen protecting group, albeit in lower yield under these conditions (entry 15).

Under the Ni(0)-catalyzed conditions, aminals with *meta*-substituted benzoyl rings cyclized to give nearly equimolar mixtures of both possible regioisomeric products. For example, aminal **1o** cyclized to give **3o** and **3o′** in 46% and 32% yield, respectively (Scheme 2). Preliminary calculations suggested that the electron-donating methoxy substituent might enable cyclization in the absence of nickel. Remarkably, cyclization of aminal **1o** not only occurred using only $MgBr_2 \cdot OEt_2$ but also gave only isoindolinone **3o**, which was isolated in 84% yield.[16] The effect of the Ni(0) catalyst on the product distribution highlights the unique role that Ni has in the formation of the isoindolinones.

Scheme 2. Cyclizations of *N*-(*m*-Methoxybenzoyl)aminal **1o** with and without Ni(0) Catalyst



The Ni(0) catalyst may either have a role in activating the C−O bond of the aminal substrate or in the C−C bond-forming step of the cyclization. To begin to differentiate between these possibilities, we determined that the cyclization of enantioenriched aminal **1a** (>99% ee) results in racemic isoindolinone **3a** (eq 1),[14] suggesting that the reaction likely proceeds via an *N*-benzoyl iminium ion. Further, heating enantioenriched **1a** with only a Lewis acid resulted in racemization of the recovered aminal (eq 2).[17,18] From this experiment, a Lewis acid alone seems sufficient to form the iminium ion. The Ni(0) catalyst then is likely involved in the C−C bond-forming step. Although it is somewhat surprising that the postulated iminium ion does not cyclize without the Ni(0) catalyst, this result is consistent with Klumpp's observation that cyclization of *N*-benzoyl iminium ions requires stoichiometric TfOH to form a superelectrophile, or doubly cationic, intermediate, which then cyclizes via a lowered transition state barrier.[8a,b] Under our conditions, Ni(0) may play a similar role in providing a lower-energy pathway for cyclization. Notably, however, Klumpp observes competing cyclization of the benzyl group to form isoindolines, instead of isoindolinones, with substrates similar to **1**. Under the Ni-catalyzed conditions, isoindolines are not observed.



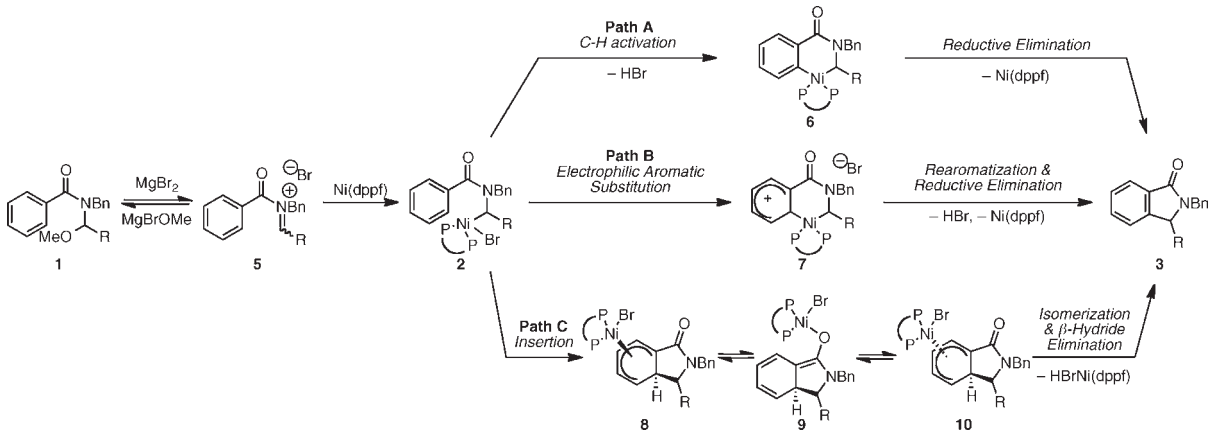
Possibilities for how Ni(0) may be involved in the C−C bond formation are shown in Scheme 3. Based on precedent

(16) The electron-donating group must be meta for cyclization to occur in high yield without Ni(0). In the presence of only $MgBr_2 \cdot OEt_2$ and no Ni(0) catalyst, the cyclization of *N*-(*p*-methoxybenzoyl)aminal **1i** resulted in only 3% yield of isoindolinone **3i**.

(17) $AlMe_3$ was used for this experiment, because $MgBr_2 \cdot OEt_2$ resulted in complete decomposition of aminal **1a**. Significant decomposition of aminal **1a** to amide **4** was observed under these conditions, but no isoindolinone **3a** was observed.

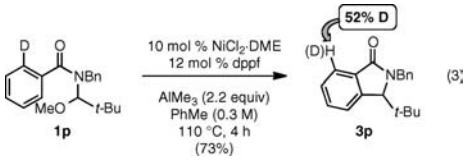
(18) This result is consistent with observations of Doyle's Ni-catalyzed cross-coupling of related aminal substrates. See ref 13.

Scheme 3. Potential Mechanisms for the Nickel-Catalyzed Cyclization



from the Arndtsen lab,[12] the electron-rich Ni(dppf) catalyst likely reacts with iminium ion **5** to form alkylnickel bromide **2**. Three distinct pathways are then possible for the C−C bond formation.[19] Via Path A, C−H activation of the benzoyl ring leads to metallocycle **6**. Subsequent reductive elimination results in isoindolinone **3**. Alternatively, electrophilic aromatic metalation of the benzoyl ring would lead to arenium ion **7** (Path B).[20] Rearomatization of intermediate **7** via deprotonation followed by reductive elimination delivers product **3**. Finally, alkylnickel species **2** may undergo a 5-exo-trig cyclization via an insertion pathway to give nickel enolate **8** (Path C). Isomerization of nickel enolate **8** via tautomer **9** would then allow isoindolinone **3** to form by β-hydride elimination. Because Pd-based catalysts can also be used for this cyclization,[14] single-electron pathways seem unlikely for this cyclization.

To test the likelihood of Path A, monodeuterated aminal **1p** was subjected to the cyclization conditions (eq 3). No intramolecular kinetic isotope effect was observed, suggesting that Path A is not the operable mechanism.[21]



Despite the different electronic requirements on the benzoyl ring, Paths B and C are more difficult to distinguish, because the electronic character of the benzoyl fragment affects both iminium formation and subsequent cyclization. Although we cannot exclude either possibility, we favor Path B, because electron-withdrawing groups on the benzoyl ring inhibit cyclization. In Path B, cyclization of the benzoyl ring may be favored over cyclization of the benzyl ring due to the conformational constraint imposed by the amide.

In summary, we have developed a 3-step procedure for the conversion of an aldehyde, amine, and benzoyl chloride to a variety of isoindolinones. The key step of this route relies on the use of an electron-rich Ni(0) catalyst to chaperone the iminium ion intermediate to the cyclized product. Studies toward exploiting this reactivity for other reactions as well as an asymmetric synthesis of isoindolinones are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, X-ray crystal structure, characterization data and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Similar mechanistic quandries have been proposed for related Pd-catalyzed cyclizations. See: (a) Martín-Matute, B.; Mateo, C.; Cárdenas, D.; Echavarren, A. *Chem.—Eur. J.* **2001**, *7*, 2341. (b) Hughes, C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. (c) Glover, B.; Harvery, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (d) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293. (e) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (f) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (g) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151.

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(21) Significant intramolecular KIEs have been observed in similar reactions that do proceed via C−H activation. See: Hennessey, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.