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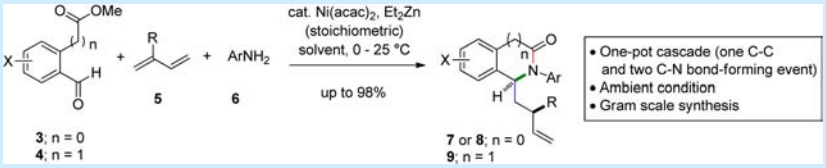
Ni(II)-Catalyzed Highly Stereo- and Regioselective Syntheses of Isoindolinones and Isoquinolinones from *in Situ* Prepared Aldimines Triggered by Homoallylation/Lactamization Cascade

Raju Karmakar,[†,§] Arun Suneja,[†,§] Vishnumaya Bisai,[†,∥] and Vinod K. Singh*[,†,‡]

[†]Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal - 462 066, Madhya Pradesh, India

[‡]Indian Institute of Technology Kanpur, Kanpur - 208 016, Uttar Pradesh, India

Supporting Information



ABSTRACT: An efficient route to isoindolinones and isoquinolinones has been achieved via a domino Ni-catalyzed homoallylation/lactamization from *in situ* prepared imines, derived from *o*-formyl benzoates and *o*-formyl arylacetates, with conjugated dienes promoted by diethylzinc. The reaction proceeds smoothly at room temperature for a variety of aldehydes, amines, and dienes. The method involves one C−C and two C−N bond forming events under operationally simple conditions.

Isoindolinones (**1a−d**; Figure 1) and tetrahydroisoquinolines (THIQs **2a−d**; Figure 1) are important heterocyclic compounds from a synthetic perspective. Many isoindolinones are useful advanced intermediates in the synthesis of a variety of drug molecules[1] and complex natural products.[2] Because of their interesting biological properties, such as antihypertensive,[3] antipsychotic,[4] anti-inflammatory,[5] anesthetic,[6] antiulcer,[7] vasodilatory,[8] antiviral,[9] and antileukemic[10] activities, these heterocyclic scaffolds are considered to be attractive synthetic targets. On the other hand, a wide variety of tetrahydroisoquinolines (THIQs **2a−d**)[11] with interesting architecture have been isolated from different sources. Due to their fascinating biological activities, THIQs also are of special synthetic interest. Needless to say, isoindolinones and THIQs constitute a common structural motif in many biologically active natural products and have become attractive synthetic targets.

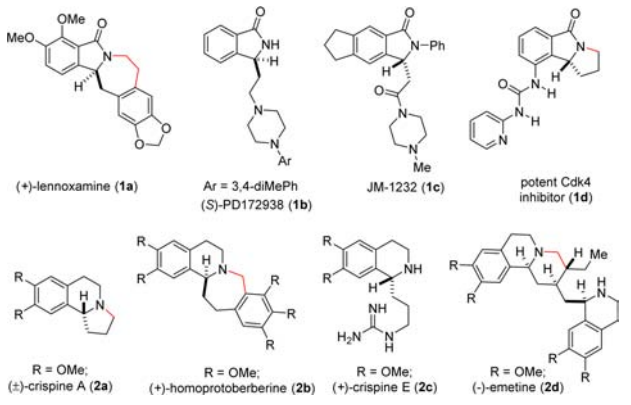


Figure 1. Selected important isoindolinones and THIQs.

Literature on existing approaches toward isoindolinone synthesis include Heck cyclization,[12] Diels−Alder approach,[13] ring closure of hydrazones,[14] reactions of acyliminium ion,[15] exploitation of carbanion methodology,[16] and various enantioselective approaches[17,18] developed very recently. On the other hand, synthesis of THIQs involves various multistep processes[11,19] and few enantioselective processes.[20] Although few elegant approaches to these targets have been reported, there is still a need to develop a straightforward synthesis of isoindolinones and THIQs employing a unified strategy from readily available simple starting materials. Toward this, we recently reported an efficient allylation−lactamization/alkylation[21] cascade in the synthesis of THIQ alkaloid (±)-crispine A (**2a**). Herein, we envision an expeditious approach to these targets following a domino Ni-catalyzed highly stereo- and regioselective homoallylation of aldimines of *o*-formyl benzoates **3** and *o*-formyl arylacetates **4** using 1,3-dienes **5** promoted by Et_2Zn to afford isoindolinones **7−8** and isoquinolinones **9**, respectively (Scheme 1).[22] Due to the low nucleophilicity and difficult availability of homoallyl metal species, unlike allylmetals, homoallylation has been less pursued. However, in the past decade, it is becoming an emerging method for the formation of C−C bonds as evident from Tamaru's work.[23a−e] Hence, we intended to explore the homoallylation strategy in the synthesis of isoindolinones and isoquinolinones.

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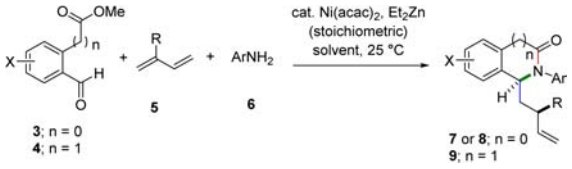
Scheme 1. Working Hypothesis



Following a $Ni(acac)_2$ catalyzed and diethylzinc mediated domino homoallylation,[23] we set forth to investigate the potential synthesis of isoindolinones **7**−**8** and isoquinolinones **9** starting from simple o-formyl benzoates **3** and *o*-formyl arylacetates **4** (Scheme 1). We started our optimization studies by using *o*-formyl methylbenzoate (**3a**), *p*-methoxyphenylamine (**6a**), and diene **5a** in the presence of $Ni(acac)_2$ and Et_2Zn to identify the standard conditions (Table 1). We used *p*-methoxyphenylamine ($PMPNH_2$, **6a**) as an amine component so as to obtain PMP-protected compound **7a**, which in turn can furnish an *N*-protecting group free isoindolinone via oxidative cleavage.[18,21,24] Following exhaustive optimization, it was found that domino homoallylation/lactamization can be realized in the presence of 10 mol % $Ni(acac)_2$ and 3.5 equiv of Et_2Zn in toluene at 0−25 °C to afford **7a** in 96% yield with 6:1 dr (standard conditions: entry 8). Gratifyingly, the reaction operates without removing water produced during condensation of *o*-formyl methylbenzoate (**3a**) and *p*-methoxyphenylamine (**6a**).

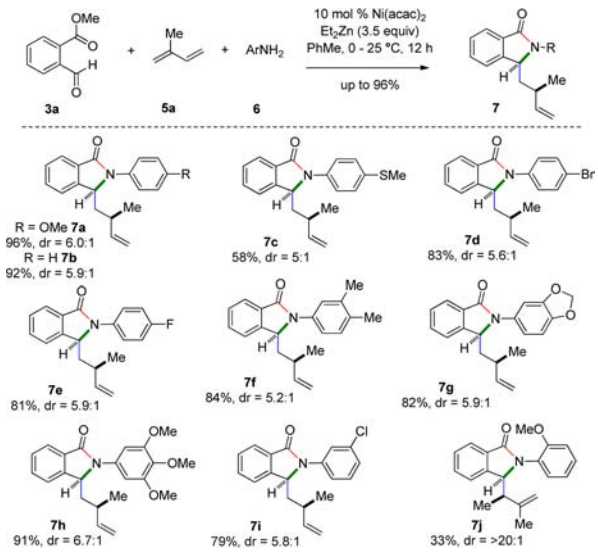
Table 1. Selected Optimization Studies of Domino Process[a]

no.	$Ni(acac)_2$ (mol %)	Et_2Zn (equiv)	solvent	temp (°C)	**7a** (%)[b]	dr[c]
1	10	3.5	THF	0−25	88	6.2:1
2	10	3.5	THF	0	78	4.8:1
3	10	3.5	THF	25	93	4.0:1
4	10	2.2	THF	0−25	43[d]	ND
5	10	3.0	THF	0−25	90	4.0:1
6	10	3.5	Et_2O	0−25	92	5.5:1
7	10	3.5	DME	0−25	89	3.4:1
8	10	3.5	PhMe	0−25	96	6.0:1
9	10	3.5	*p*-xylene	0−25	93	5.4:1
10	5	3.5	PhMe	0−25	85	6.2:1
11	5	1.8	PhMe	0−25	72	6.0:1

[a]Reactions were carried out on 1.0 mmol of **3a** and PMP-NH_2 **6a** in the presence of 4.0 equiv of diene **5a**, 3.5 equiv of Et_2Zn, and 10 mol % of $Ni(acac)_2$ in 3 mL of solvent at indicated temperature. [b]Isolated yields after column purification. [c]dr's were determined from ^1H NMR of crude materials. [d]Decomposition of the rest of the mass balance. CCDC number of **7a**: 1427165 [see Supporting Information for details].

With the standard conditions in hand, we explored the synthetic viability of the domino homoallylation/lactamization process using *o*-formyl methylbenzoate (**3a**) and isoprene (**5a**), with a variety of aromatic amines. Scheme 2 demonstrates the scope of the reaction encompassing different kinds of aromatic amines to provide isoindolinones **7b**−**j**. Aromatic amines having electron-deficient as well as electron-rich substituents afforded products **7b**−**e** in high yields with a maximum of 5.9:1 dr. It was noteworthy that other electron-rich aromatic amines, such as 3,4-dimethylaniline, 3,4-methylenedioxy aniline, and 3,4,5-trimethoxyaniline, were excellent amine partners for the domino process to afford isoindolinones **7f**−**h** in up to 91% yields with a maximum of 6.7:1 dr. *m*-Chloroaniline afforded **7i** in 79% yield with 5.8:1 dr. Interestingly, some anomality was observed in the case of *o*-substituted anilines, such as 2-methoxy aniline. Instead of the desired terminal attack by diene, an internal attack is observed. This afforded isoindolinone **7j** in excellent dr (>20:1) albeit in low yield (33%), probably indicating that sterics play an important role in the one-pot homoallylation/lactamization process.

Scheme 2. Effect of Different Aromatic Amines on Isoindolinone Synthesis[a]



[a]Reactions were carried out on a 1.0 mmol of each **3a** and amine **6** in the presence of 4.0 equiv of diene **5a** in 3 mL of solvent at indicated temperature. Isolated yields after column purification are shown. dr's were determined from ^1H NMR of crude materials.

We further expanded the substrates scope of the domino one-pot homoallylation/lactamization using a variety *o*-formyl benzoates **3** having different electronic properties (Scheme 3). *o*-Formyl benzoates **3** having different halogen functionalities afforded products **7k** and **7n**−**o** in synthetically viable yields with up to 10:1 dr.

It was also observed that substrate **3** sharing a phenyl ring was also a good substrate, which afforded products **7l** and **7m** in up to 76% yields with up to 5.9:1 dr. Substrate **3** having highly electron-rich functionality furnished **7p**−**q** in 75% and 62% yield respectively with up to 4.3:1 dr. On the other hand, substrates bearing electron-withdrawing groups (e.g., 5-NO_2, 4-CN of **3** in Scheme 3) failed to provide the desired product, giving a complex mixture.

Next, different dienes were also employed under standard conditions, which furnished products in good to excellent yields. Cyclohexane-1,3-diene afforded **8a** in 58% yield with excellent dr (>20:1; Scheme 4). The reaction is highly regioselective in nature, where *β*-myrcene afforded isoindolinones **8b**−**c** in 73−98% yield (dr up to 7.1:1). A diene consisting of an aromatic ring *viz. trans*-1-phenyl-1,3-butadiene also provided the desired product **8d**.

In a few cases, an anomalous reaction was observed during the reaction. *o*-Methoxy aniline furnished reductive amination product **10b** (Scheme 5) along with **7j** (Scheme 2). In fact,

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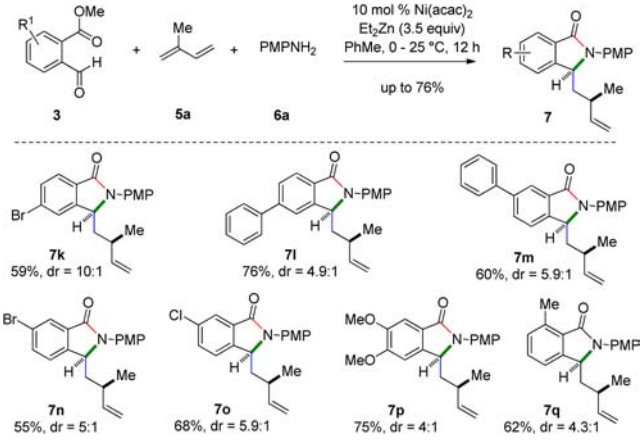
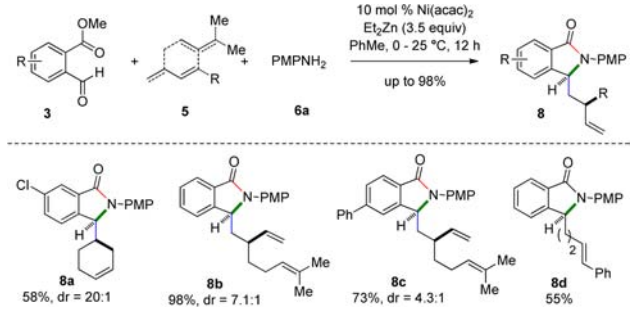
Scheme 3. Substrate Scope of Isoindolinone Synthesis[a]



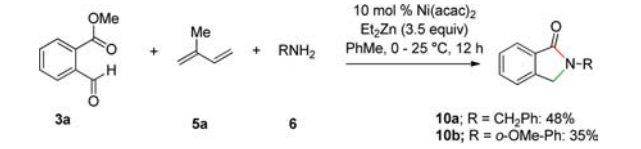
[a]See Scheme 2 footnote for details.

Scheme 4. Isoindolinone Synthesis with Varied Dienes[a]



[a]See Scheme 2 footnote for details.

Scheme 5. Reductive Amination under Optimized Condition

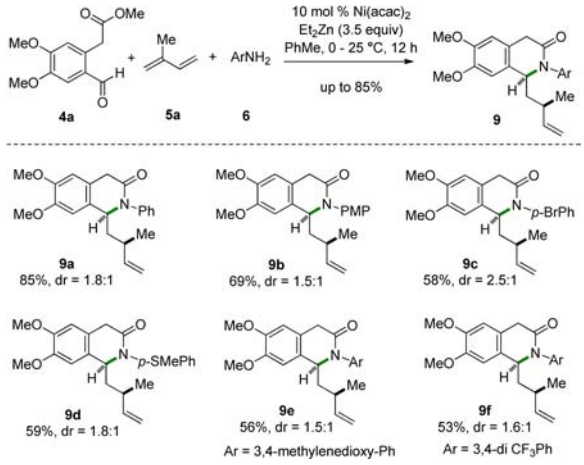


reductive amination was prominent when an aliphatic amine was used as a coupling partner yielding *N*-benzylisoindolin-1-one (**10a**), clearly indicating that the basicity/nucleophilicity of amine partners play a crucial role in switching the reactivities.

Later, the subset of tetrahydroisoquinolines (THIQs; Figure 1) which constitute a common structural motif in many biologically active alkaloids drew our attention. We reasoned that isoquinolinones can play a crucial role in synthesizing a variety of THIQs via synthetic manipulations. Thus, Ni-catalyzed domino homoallylation/lactamization of imines prepared from *o*-formyl arylacetate **4a** and amine **6** with conjugated diene **5a** promoted by diethylzinc was carried out further (Scheme 6). Delightfully, a variety of isoquinolinones **9a**–**f** with various amide functionalities were synthesized under the standard conditions in synthetically useful yields with up to 2.5:1 dr. We believe that these compounds have the potential for the synthesis of a range of advanced intermediates for the total synthesis of isoquinoline alkaloids.

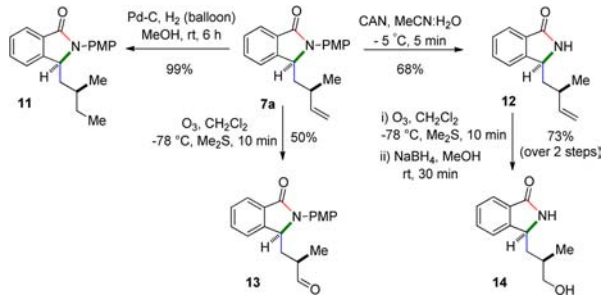
With a synthetically viable route to the isoindolinones and isoquinolinones in hand, we were inclined to elaborate these compounds to the various synthetic intermediates (Scheme 7). Toward this end, we performed hydrogenation of compound **7a**

Scheme 6. Effect of Different Aromatic Amines on Isoquinolinone Synthesis[a]



[a]Reactions were carried out on a 1.0 mmol of each **4a** and amine **6** in the presence of 4.0 equiv of diene **5a** in 3 mL of solvent at indicated temperature. Isolated yields after column purification are shown. dr's were determined from ^{1}H NMR of crude materials.

Scheme 7. Synthetic Elaboration of Domino Product



to afford **11** in quantitative yield. Again, **7a** was converted to aldehyde **13** via oxidative cleavage of terminal olefin. In another sequence, we have also shown that deprotection of PMP group of **7a** can be carried out to obtain free amide **12** (Scheme 7), which further transformed to **14** in 73% yield, via reductive ozonolysis.

In conclusion, domino Ni-catalyzed regio- and stereoselective homoallylation/lactamization of aldimines (*in situ*) of *o*-formyl benzoates **3** and aromatic amines has been developed. The salient features of this process are the highly regio- and stereoselective nature to provide 1,3-*syn*-selectivity, the reaction is completed at room temperature, diverse substrates with electron-donating and -withdrawing functionality can give satisfactory results, and the reaction can be operated on a gram scale (see Supporting Information for details). Further, we have explored the method for stereoselective synthesis of isoquinolinones from aldimine prepared from *o*-formyl arylacetate **4a**. We believe that an enantioselective version of this method would serve as a potential strategy to access isoindolinones and isoquinolinones in an enantioenriched form. These are under active investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and analytical data (^{1}H, ^{13}C NMR spectra and HRMS) for all new compounds (PDF)
X-ray data for **7a** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: vinodks@iitk.ac.in.

Present Address

[‖]Department of Chemistry, Indian Institute of Science Education and Research Tirupati, Karakambadi Road, Mangalam, Tirupati - 517 507, Andhra Pradesh, India.

Author Contributions

[§]R.K. and A.S. contributed equally.

Notes

The authors declare no competing financial interest.

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