Asymmetric Catalysis

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Asymmetric Alkynylation/Lactamization Cascade: An Expeditious Entry to Enantiomerically Enriched Isoindolinones**

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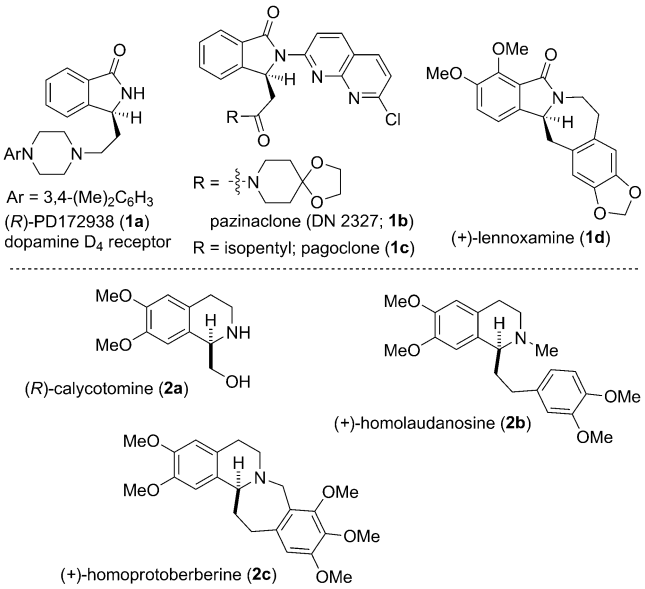
Dedicated to Professor Sukh Dev on the occasion of his 90th birthday

Abstract: *An unprecedented Cu^{I}–pybox-diPh-catalyzed highly enantioselective (up to >99% ee) alkynylation/lactamization cascade has been developed as a general catalytic system for the synthesis of diversely substituted isoindolinones of immense biological importance. The cascade effects one C–C and two C–N bond-forming events in one reaction vessel under operationally simple, additive-free reaction conditions in good to excellent yields. The methodology was further extended to the synthesis of tetrahydroisoquinoline scaffolds common to several biologically active natural products in a two-step sequence with remarkable selectivity (up to 94% ee).*

Enantiomerically enriched isoindolinones are an important class of synthetically useful heterocyclic compounds (Scheme 1, **1a–d**) with an impressive diversity of biological activity. Their biological potential is evident from observed antihypertensive,[1] antipsychotic,[2] anti-inflammatory,[3] anesthetic,[4] antiulcer,[5] vasodilatory,[6] antiviral,[7] and antileukemic[8a] activity. Some of these compounds show platelet-aggregation-inhibitory activity.[8b] A few isoindolinones were also found to induce dose-dependent p53-dependent gene transcription in MDM2-amplified SJSA human sarcoma cell lines.[9] Furthermore, these compounds are also useful in the synthesis of various drugs[10] and complex natural products.[11] On the other hand, tetrahydroisoquinoline rings exist widely in alkaloids and their derivatives (Scheme 1, **2a–c**),[12] which display numerous types of biological activity. Although a few elegant approaches to these targets have been reported, there is no evidence of a straightforward synthesis of isoindolinones and tetrahydroisoquinolines (THIQs) by a unified strategy from simple and readily available starting materials.



Scheme 1. Selected isoindolinones and tetrahydroisoquinolinones **1** and **2**.

Prominent examples of asymmetric approaches to isoindolinone synthesis involve the resolution of racemates,[13] an intramolecular Heck cyclization,[14] an asymmetric Diels–Alder approach,[15] the ring-closure of chiral hydrazones,[16] reactions of chiral acyliminium ions,[17] and a chiral-appendage-mediated carbanion method.[18] On the other hand, syntheses of enantiomerically enriched THIQs involve various diastereoselective processes[12,19] and catalytic enantioselective processes. The latter include the ruthenium-catalyzed hydrogenation of preformed *N*-alkyl enamides and *N*-alkyl imines,[20] the copper-catalyzed allylation of cyclic imines[21] and terminal alkynes to give isoquinoline iminium ions,[22] and palladium-catalyzed intramolecular allylic amination.[23]

In pursuit of a practical and efficient approach to enantiomerically enriched isoindolinones and isoquinolinones, we envisaged a modular route involving an enantioselective copper(I)-catalyzed one-pot alkynylation/lactamization[24,25] cascade of readily available *o*-formyl methyl benzoates **3** and *o*-formyl methyl arylacetates **7** (Scheme 2). We delineate herein the first example of a copper(I)-catalyzed alkynylation/lactamization cascade with an exceptionally high level of enantioselectivity.

At the outset, we studied several potential catalysts to ultimately identify the most efficient catalytic system for this transformation (Scheme 3). As a model system for the

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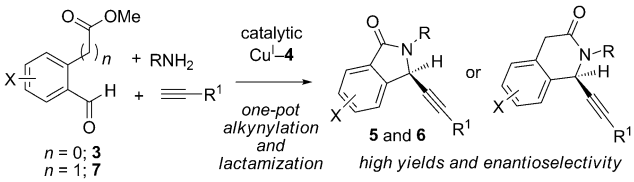
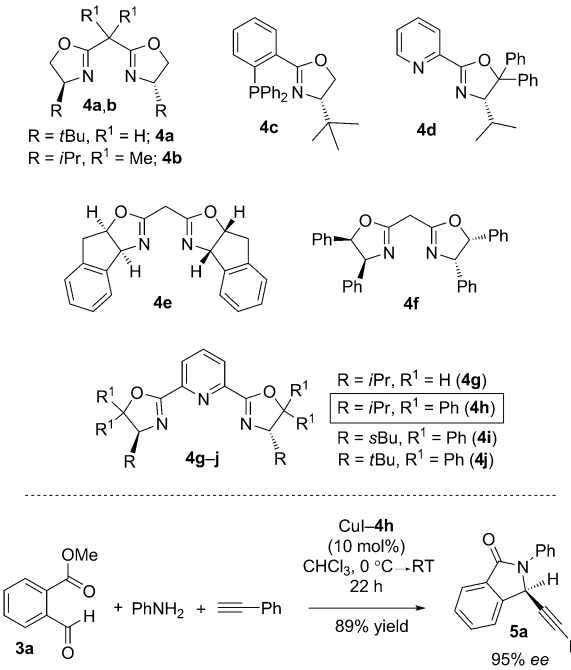


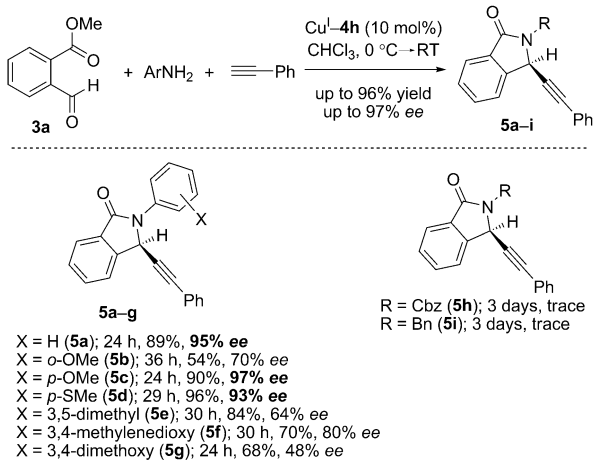
Scheme 2. Proposed copper(I)-catalyzed alkynylation/lactamization cascade.



Scheme 3. Optimization studies with various ligands **4a–j**.

synthesis of isoindolinone derivatives, we initially carried out the copper(I)-catalyzed alkynylation/lactamization cascade with methyl 2-formylbenzoate (**3a**), aniline, and phenylacetylene in the presence of Cu^I–**4a–j** (10 mol%) in chloroform at room temperature under an inert atmosphere. We found that Cu^I complexes of oxazoline and bisoxazoline catalysts, that is, Cu^I–**4a–f** (Scheme 3) either did not promote this reaction or furnished **5a** in low yields with low enantioselectivity (see the Supporting Information for details). However, the Cu^I complex of *i*Pr-pybox, Cu^I–**4g**, afforded isoindolinone **5a** in 60% yield with 42% *ee*. Following extensive optimization, we found that the alkynylation/lactamization cascade occurred efficiently in the presence of 10 mol% of Cu^I–pybox catalysts with *gem*-diphenyl groups (ligands **4h–j**), that is, Cu^I–**4h–j**, to afford **5a** in 92, 87, and 89% yield with 93, 86, and 88% *ee*, respectively. By brief solvent screening with the most effective ligand, **4h**, we found chloroform to be the best solvent in terms of both yield and enantioselectivity. Temperature studies indicated that the product was obtained in good yield with excellent enantioselectivity when the reaction was conducted at 0–25 °C. Lowering of the catalyst loading to 5 mol% led to slower reaction rates. Interestingly, the product was also formed with high enantioselectivity (91% *ee*) when Cu^{II}–*i*Pr-pybox-diPh (Cu^{II}–**4h**) was used as the catalyst (see the Supporting Information for details).

A close inspection of the scope and limitations of the reaction under the optimized conditions with various amines (Scheme 4) revealed that aromatic amines containing electron-donating groups gave the desired isoindolinones **5**. For

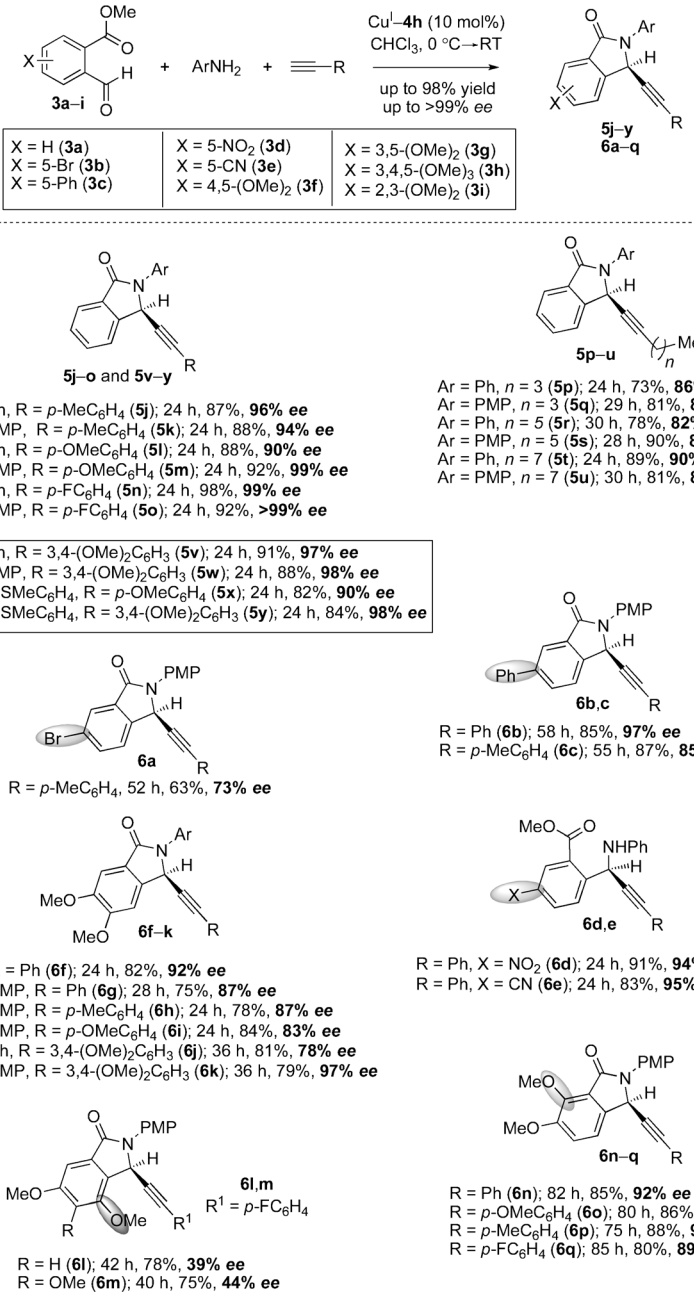


Scheme 4. Optimization with various amine components. Bn = benzyl, Cbz = carboxybenzyl.

example, the use of 4-methoxyaniline afforded isoindolinone **5c** with 97% *ee* (90% yield). Such *N*-aryl substituents with electron-donating groups could be oxidatively cleaved to access unprotected isoindolinones. The reaction with an aromatic amine bearing an *ortho* substituent was sluggish and furnished product **5b** with a lower *ee* value. In the case of the less nucleophilic amine $CbzNH_2$,[26] we did not obtain the desired product. Instead, the starting 2-formylbenzoate **3a** and $CbzNH_2$ were isolated in 70–79% yield. However, in the case of more basic benzylamine, the reaction led to a multitude of TLC spots, thus indicating the requirement of selective amines in the alkynylation/lactamization cascade. We investigated the scalability of the reaction on a gram scale with **3a** (1.0 g), aniline, and phenylacetylene, under which conditions we obtained **5a** with 92% *ee* (48 h, 87% yield).

With aniline and *p*-anisidine as amines of choice, the alkynylation/lactamization cascade was further extended to a variety of terminal alkynes (Scheme 5). A wide range of terminal alkynes bearing an aromatic ring or an aliphatic side chain could be used under the optimized conditions to obtain enantiomerically enriched isoindolinones with good to excellent enantioselectivity. Notably, terminal alkynes with aromatic rings containing both electron-donating and electron-withdrawing groups afforded products **5j–o** with high enantioselectivity (up to > 99% *ee*). Even with aliphatic terminal alkynes, the process afforded products **5p–u** with *ee* values in the range of 82–90%. The reaction was also highly efficient when electron-rich *p*-thiomethoxyphenylamine used as the amine component; in this case, isoindolinone products **5x** and **5y** were obtained with 90 and 98% *ee*, respectively.

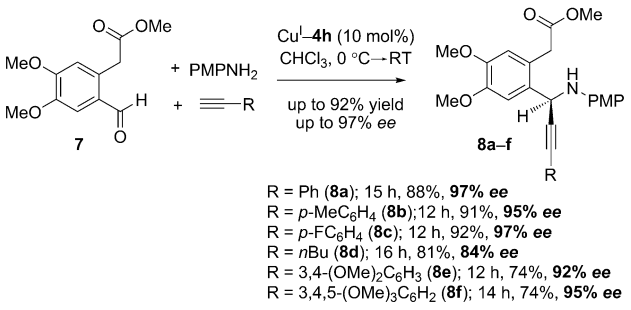
Next, we explored the scope of the reaction with a variety of methyl 2-formylbenzoates, **3b–i** (Scheme 5). Methyl 5-



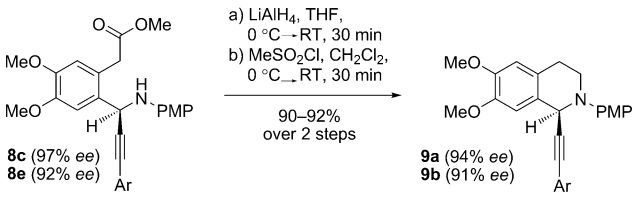
Scheme 5. Scope of the reaction with methyl 2-formylbenzoates **3a–i**. PMP = *p*-methoxyphenyl.

bromo-2-formylbenzoate (**3b**) was transformed into product **6a** in 63% yield with 73% *ee*. In the case of the 5-phenyl-substituted aldehyde **3c**, isoindolinones **6b** and **6c** were obtained in 85 and 87% yield, respectively, with up to 97% *ee*. Evidently, an electron-withdrawing group at the *para* position with respect to the aldehyde functionality (substrates **3d**,**e**) hampers the formation of isoindolinones. We could only isolate **6d** and **6e** in 83 and 91% yield with 94 and 95% *ee*, respectively, thus indicating the less nucleophilic nature of the secondary aromatic amines owing to the presence of electron-withdrawing groups. Gratifyingly, methyl 2-formylbenzoate **3g** with an electron-donating methoxy group at the *para* position was a good precursor and afforded a variety of isoindolinones **6f–k** in 75–84% yield with 78–97% *ee* with various terminal alkynes.[27] Notably, aldehydes **3g**,**h** with an *o*-methoxy group were found to be inferior and afforded isoindolines **6l** and **6m** with only 39 and 44% *ee*, thus indicating that steric hindrance at the *ortho* position to the aldehyde has a crucial effect on the enantioselectivity of product formation. Importantly, methyl 2,3-dimethoxy-2-formylbenzoate (**3i**) afforded products **6n–q** with 88–92% *ee* (Scheme 5). These compounds could serve as advanced intermediates in the synthesis of (+)-lennoxamine (**1d**) and related structures (Scheme 1).

The aforementioned results called for the extension of our strategy to the enantioselective synthesis of C_1-substituted isoquinolinones for the eventual construction of various synthetically important tetrahydroisoquinolines (THIQs) (Scheme 1).[12b] To this end, the direct Cu^I–**4h**-catalyzed alkynylation/lactamization cascade was carried out on methyl (6-formyl-3,4-dimethoxyphenyl)acetate (**7**; Scheme 6). However, the results were disappointing: Only uncyclized products were formed, but in fairly good yields and with excellent enantioselectivity (up to 97% *ee*). We surmised that the less nucleophilic nature of the secondary aromatic amine might require additional energy to form a six-membered structure, thus restricting the lactamization step. In contrast, in the case of isoindolinones, the lactamization is facile, probably owing to the formation of the five-membered isoindolinone ring. However, our alkynylation process could be used to access a diverse array of tetrahydroisoquinoline alkaloids shown in Scheme 1 by a two-step synthetic elaboration involving reduction of the ester followed by mesylation, without much compromise in the enantiomeric purity of the product (Scheme 7). Compounds **9** could serve as advanced intermediates for the synthesis of natural products **2a–c** through



Scheme 6. Scope of the reaction with the ester–aldehyde **7**.

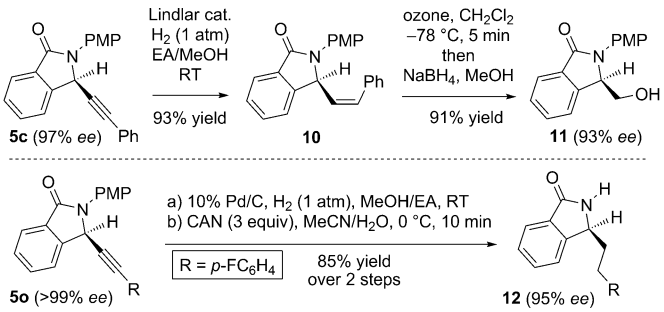


Scheme 7. Synthetic elaboration to enantiomerically enriched THIQs.

simple synthetic elaboration by exploiting the unique reactivity of the triple-bond functionality.

The absolute configuration of the products was unambiguously assigned as "*S*" on the basis of the X-ray crystal structures of compounds **5y** (CCDC 1000307) and **8a** (CCDC 1000308; see the Supporting Information).

Finally, the usefulness of this process was highlighted by partial hydrogenation of the triple-bond functionality of **5c** (97% *ee*) to give **10**, which underwent reductive ozonolysis to afford the hydroxymethyl derivative **11** with 93% *ee*. Compound **11** could serve as an advanced intermediate for the synthesis of **1a–c**. Furthermore, complete hydrogenation of **5o** followed by oxidative cleavage of the *N*-PMP group[28] in the presence of CAN afforded enantiomerically enriched **12** in 85% yield over two steps (Scheme 8).



Scheme 8. Synthetic elaboration to important intermediates. CAN = ceric ammonium nitrate, EA = ethyl acetate.

In conclusion, we have reported the first highly enantioselective one-pot alkynylation/lactamization cascade as a new entry to a wide range of isoindolinones. The operational simplicity of the method and its amenability to gram-scale synthesis, as well as the straightforward access it provides to enantiomerically enriched isoindolinones with unprecedented levels of enantioselectivity (up to > 99% *ee*) under additive-free conditions, makes our strategy highly viable. Furthermore, its application is illustrated in the synthesis of optically pure THIQs (up to 94% *ee*) in a two-step procedure. The usefulness of the methodology has also been demonstrated by cleavage of the *N*-PMP group and by exploiting the reactivity of the triple bond. This concise and flexible synthetic route offers ample opportunity for its application in the synthesis of complex natural products, which is currently being pursued in our laboratory.

Experimental Section

A solution of a ligand **4h** (0.03 mmol, 10 mol%) and $(CuOTf)_2$·PhMe complex (0.03 mmol, 10 mol%) in dry chloroform (3 mL) was stirred at 0°C for 30 min under a nitrogen atmosphere. An aldehyde (0.3 mmol) and an aromatic amine (0.3 mmol) were added, and the resulting mixture was stirred for an additional 15 min. An alkyne (0.45 mmol) was then added at the same temperature, and the reaction mixture was allowed to warm to 25°C. After completion of the reaction (monitored by TLC), the mixture was concentrated in vacuo and purified over silica gel by column chromatography (15–40% EtOAc in hexane) to afford products in up to 98% yield with up to > 99% *ee*.

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