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Copper Catalyzed One-Pot Three-Component Imination−Alkynylation−aza-Michael Sequence: Enantio- and Diastereoselective Syntheses of 1,3-Disubstituted Isoindolines and Tetrahydroisoquinolines

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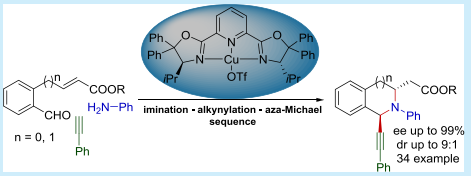
Supporting Information

ABSTRACT: An enantio- and diastereoselective syntheses of 1, 3-disubstituted isoindolines and tetrahydroisoquinolines via Cu^{I}-Pybox-diPh catalyzed one-pot imination−alkynylation−aza-Michael sequence has been reported. The three-component reaction produces one C−C and two C−N bonds sequentially with high yield (up to 92%), enantioselectivity (up to 99%), and diastereoselectivity (up to 9:1) in a single operation. Furthermore, the synthetic utility of the product has been demonstrated by $LiAlH_4$ reduction of ester and hydrogenation of alkyne functionality without losing the stereoselectivity.

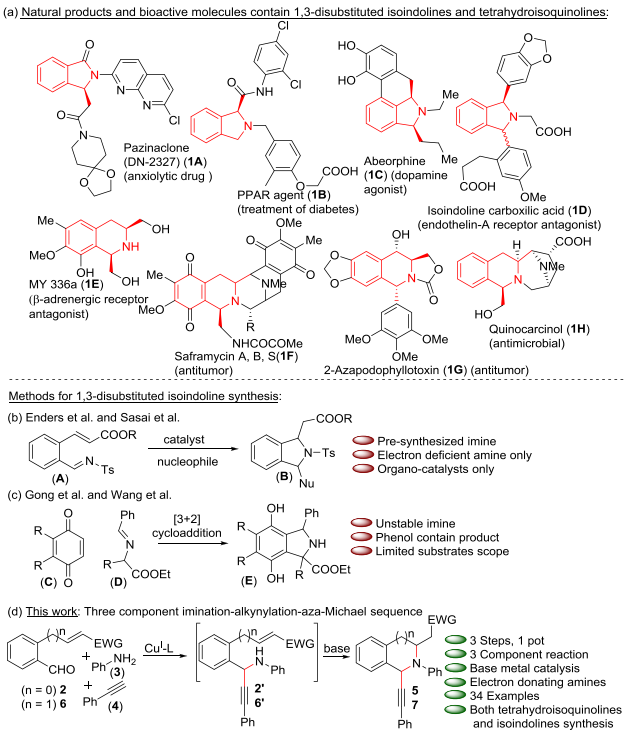


An asymmetric multicomponent reaction sequence is a very attractive method because of its ability to construct complex chiral molecules in a single operation from readily available substrates in two or more steps under mild, one-pot reaction conditions. These reactions can eliminate the tedious process of isolation/purification of the synthetic intermediates as well as save time and chemicals by reducing steps. During the past decades, asymmetric multicomponent reaction sequences have emerged as a powerful tool for the construction of heterocycles.[1]

Enantioenriched substituted isoindolines and tetrahydroisoquinolines (THIQ) are an essential class of synthetically useful heterocyclic compounds (Scheme 1a) with impressive applications in pharmaceuticals, natural products, and biologically active molecules.[2] Their biological potential manifests from observed anxiolytic,[3] antidiabatic,[4] and dopaminergic[5] activity. Some of these compounds show as a potent endothelin-A[6] selective receptor antagonist. On the other hand, biologically important disubstituted tetrahydroisoquinolines display β-adrenergic receptor[7] antagonist, antitumor,[8,9] and antimicrobial[10] activities.

Because of these important factors, several approaches were made for the synthesis of unsubstituted[11] and monosubstituted isoindolines,[12] but only a few methods have been reported for the catalytic asymmetric synthesis of 1,3-disubstituted isoindolines in an enantio- and diastereoselective manner. Other than chiral pool synthesis,[13] two types of catalytic approaches have been made. First one, was the nucleophilic addition to the presynthesized imine (Scheme 1b) followed by cyclization, reported by the Enders[14] and Sasai[15] groups. Pre-synthesized imine as starting material restricts the versatility of the method. Both reports use an organocatalyst, and in some cases, reaction required 10 days to obtain a reasonable outcome. The other approach was a [3 + 2] cycloaddition (Scheme 1c) of the azomethine ylide (**D**) with quinone (**C**) in the presence of chiral catalysts, reported by Gong[16] and Wang[17] et al. Major

Scheme 1. Structure of Related Bioactive Molecules (a); Synthetic Routes of 1,3-Substituted Isoindolines (b, c, d)



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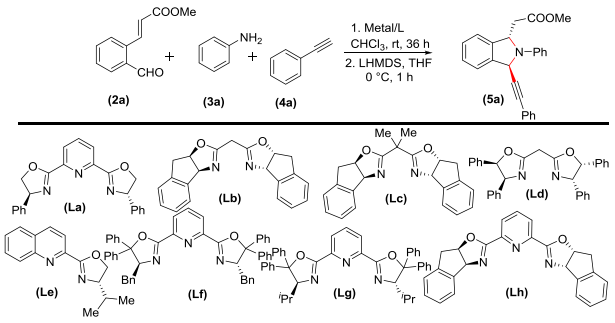
disadvantages of this process include the instability of the starting materials and requirement of multiple steps in the synthesis. Also, the product contains a *p*-hydroxy phenol derivative, which can make it more difficult for further functionalization.

On the other hand, there are some elegant methods reported for the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines in a stereoselective manner. Studies have been reported by Enders,[18] Liu,[19] Yamamoto,[20] Ferraccioli,[21] and Zhou[22] with different organometallic catalysts.

Other than these few approaches toward individual synthesis of disubstituted isoindolines and tetrahydroisoquinolines, no such straightforward synthetic methodology has been reported which includes both 1,3-disubstituted isoindoline and tetrahydroisoquinoline synthesis *via* the same operation from simple, stable, and readily available starting materials. In this context, here, we report a Cu^{I}-Pybox-diPh catalyzed one-pot imination−alkynylation−aza-Michael sequence for the synthesis of enantio- and diastereoselective 1,3-disubstituted isoindolines and tetrahydroisoquinolines. A multicomponent reaction occurs sequentially *via* copper-catalyzed imine formation (Scheme 1d) from the aldehyde functionality of 2-formylphenyl acrylate **2** or 2-formylphenyl crotonate **6** and aniline **3**, followed by asymmetric alkynylation with phenylacetylene **4** producing the intermediate **2′** or **6′**. The intermediate undergoes base-promoted aza-Michael cyclization in the same reaction vessel and leads to the desired product **5** or **7** with an exceptionally high level of yield as well as enantio- and diastereoselectivity. Three elementary steps proceed in one pot by generating one C−C and two C−N bonds, simultaneously.

Several potential catalysts were screened for the synthesis of 1,3-disubstituted isoindoline **5a** *via* a three-component imination−alkynylation−aza-Michael sequence in the presence of pybox ligand **La** with 2-formylphenyl acrylate **2a**, aniline **3a**, and phenyl acetylene **4a** (Table 1, entries 1−5) as model substrates. Only Cu^{I}-triflate and Cu^{II}-triflate produced the desired product with yields of 41% and 35% and enantioselectivities of 68% and 65%, respectively. Other catalysts such as $Sc(OTf)_2$, $Zn(OTf)_2$, etc. failed to catalyze the reaction. Therefore, further study was carried out in the presence of Cu^{I}-triflate (10 mol %) with different oxazoline ligands in chloroform at room temperature under an inert atmosphere. Cu^{I}-complexes of Ligand **Lb-e** either did not initiate the reaction or furnished **5a** in very low yield (<20%). However, the Cu^{I}-complexes of ligand **Lf-g**, Cu^{I}-Pybox-diPh, afforded **5a** in up to 82% yield with 90% ee and 8:1 dr (Table 1, entries 8−9). Here, the noticeable improvement in yield and selectivity was found by using the modified Pybox ligands **Lf-g**. This modification was first made by our group to improve the steric and electronic nature of the ligand by introducing diaryl substitution on the 5-position of oxazoline which gave the best result in the Cu^{I}-catalyzed propargylation reaction.[23] Extensive temperature and solvent study indicated that the imination−alkynylation occurs best at room temperature in toluene, but the final product was obtained in optimal yield on exposure of the reaction mixture to an equimolar solution of lithium hexamethyldisilyl amide (LHMDS)[24] in THF at 0 °C. Thus, the isoindoline **5a** was isolated in 85% yield and 91% ee with a diastereomeric ratio of 9:1 (Table 1, entry 12) (see Supporting Information for complete screening). Lowering the catalyst loading to 5 mol % led to a slower reaction rate.

Table 1. Optimization of Reaction Conditions[a]

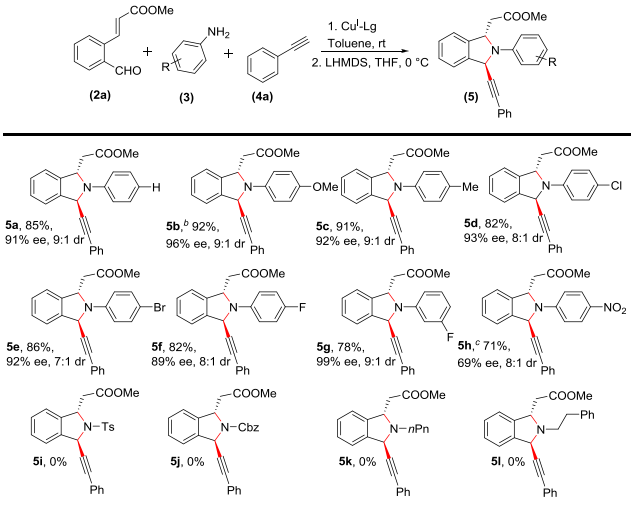


entry	catalyst	L	yield (%)[b]	ee (%)[c]	dr[b]
1	$Sc(OTf)_2$	**La**	<20	–	–
2	$Zn(OTf)_2$	**La**	<20	–	–
3	$Cu(CH_3CN)_4PF_6$	**La**	<20	–	–
4	$Cu(OTf)_2$	**La**	35	65	4:1
5	$(CuOTf)_2{\cdot}C_6H_6$	**La**	41	68	4:1
6	$(CuOTf)_2{\cdot}C_6H_6$	**Lb**	<20	–	–
7	$(CuOTf)_2{\cdot}C_6H_6$	**Lc**	<20	–	–
8	$(CuOTf)_2{\cdot}C_6H_6$	**Lf**	75	62	4:1
9	$(CuOTf)_2{\cdot}C_6H_6$	**Lg**	82	90	8:1
10[d]	$(CuOTf)_2{\cdot}C_6H_6$	**Lg**	55	85	7:1
11[e]	$(CuOTf)_2{\cdot}C_6H_6$	**Lg**	0	–	–
12[f]	$(CuOTf)_2{\cdot}C_6H_6$	**Lg**	87(85)[g]	91	9:1

[a]Reaction conditions: **2a** (0.2 mmol, 1 equiv), **3a** (0.22 mmol, 1.1 equiv), **4a** (0.3 mmol, 1.5 equiv), metal (10 mol %), ligand (11 mol %), base (0.2 mmol, 1 equiv), solvent (2 mL). [b]Yield and dr were determined from ^{1}H NMR of the crude reaction mixture with acenaphthene as an internal standard. [c]Ee was determined by HPLC analysis using chiral column. [d]CH_2Cl_2 was used as solvent. [e]CH_3CN was used as solvent. [f]Toluene was used as solvent. [g]Isolated yield in parentheses.

Scope and limitations of the reaction under the optimized conditions with various amines (Scheme 2) revealed that aromatic amines containing an electron-donating group improve the yield and enantioselectivity of the reaction. 4-

Scheme 2. Substrate Scope of Anilines[a]



[a]Reaction conditions were same as those for Table 1, unless otherwise noted. [b]The reaction was carried out also in 2 mmol scale. [c]Reaction was carried out at 50 °C.

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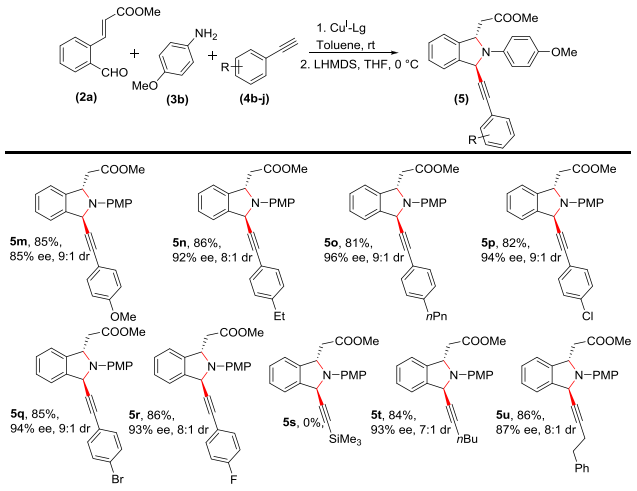
Methoxy and 4-methyl aniline afforded isoindolines **5b–c** in more than 90% yields with 96% and 92% ee's, respectively. Different halide substituted anilines resulted in excellent yields and enantioselectivities. For 3-fluoro aniline, the reaction was quite slow (78% yield of **5g**), but the enantioselectivity was excellent (99% ee). All the substituted anilines gave very high enantioselectivities and up to 9:1 diastereoselectivities, except 4-nitroaniline, which required a higher temperature (50 °C) for imination and alkynation reactions. A few electron-deficient amines, e.g., $TsNH_2$, $CbzNH_2$, etc., have also been investigated, but these were unable to form imine in the given reaction conditions. It might be due to their electron-deficient nature. We have carried this imination–alkynylation–aza-Michael sequence with alkyl amines such as *n*-pentyl amine and phenylethyl amine. Unfortunately, the desired products **5k–l** were not formed and we have ended up with a complex mixture of products. To demonstrate practical usefulness, the reaction was scaled up to 2 mmol scale, and the product **5b** was obtained with the same level of yield and enantioselectivity.

Since 4-methoxyaniline gave a higher yield and enantioselectivity, the three-component imination–alkynylation–aza-Michael sequence was further extended to a variety of terminal alkynes (Scheme 3) with this amine. There were no significant

Scheme 3. Substrate Scope of Alkynes[a]

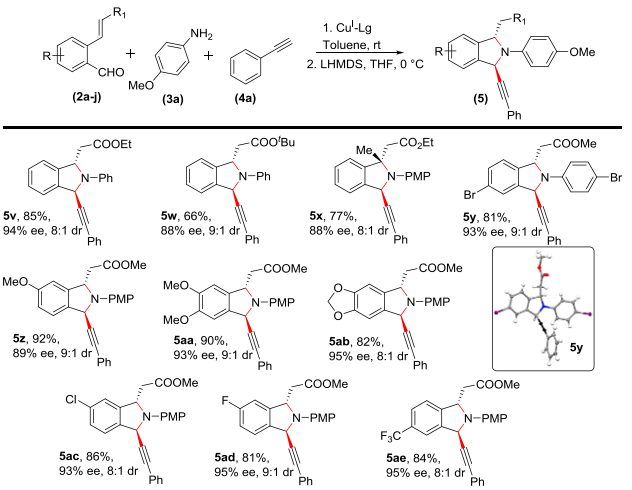


[a]Reaction conditions were same as those for Table 1, unless otherwise noted.

changes in yields and selectivities by changing the electronic nature of the substitution on the aromatic ring of alkyne. The corresponding isoindolines **5m–r** were obtained in high yields, up to 86%, and ee's up to 96% with good diastereoselectivities. A differently substituted alkyne, such as trimethylsilyl acetylene, was unable to produce **5s**. Only the imine formation was observed in the reaction mixture. The reaction was also smooth for aliphatic terminal alkynes, generating the corresponding isoindolines **5t–u** with high yields (84% and 86%, respectively) and enantioselectivities (93% and 87%, respectively).

Next, we explored the scope of the reaction by installing a variety of functional groups in aldehyde **2** (Scheme 4). Different ester functionalities, e.g., ethyl ester, gave the corresponding isoindoline **5v** in very good yield (85%) and enantioselectivity (94%). Sterically bulky *tert*-butyl ester

Scheme 4. Substrate Scope of Aldehydes[a]



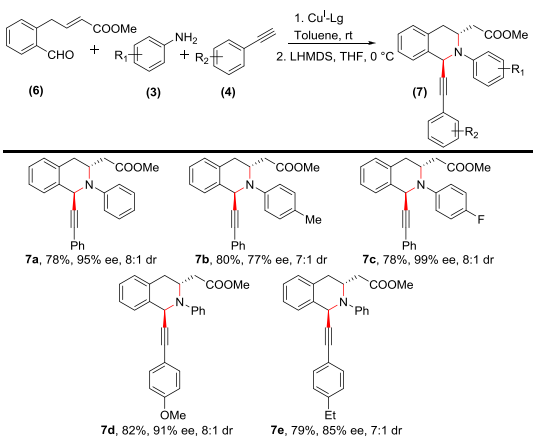
[a]Reaction conditions were same as those for Table 1, unless otherwise noted.

provided isoindoline **5w** in comparatively lower yield (66%) with 88% ee. A quaternary carbon center was generated in isoindoline **5x** without affecting the stereoselectivity of the reaction. When different substitution in the aromatic ring of 2-formylphenyl acrylate **2** was introduced, no significant change was observed in yields (up to 92%) as well as enantio- (up to 95%) and diastereoselectivities (up to 9:1) of isoindolines **5y–ae** (Scheme 4).

The absolute configuration of the product was assigned as (*S*, *S*) based on the X-ray crystal structure analysis of **5y** (CCDC 1893283; see Supporting Information).

After successful synthesis of isoindolines, we then turned our focus toward 1,3-disubstituted tetrahydroisoquinolines (THIQ), starting from 2-formylphenyl crotonate **6** (Scheme 5). Different amines, such as aniline, 4-methyl, and 4-fluoro aniline, produced the corresponding tetrahydroisoquinolines **7a–c** with yields up to 80%, enantioselectivities up to 99%, and dr's up to 8:1. Various alkynes were also examined and afforded tetrahydroisoquinolines **7d–e** with yields up to 82% and enantioselectivities up to 91% via the Cu^I-Pybox-diPh

Scheme 5. Synthesis of 1,3-Disubstituted Isoquinolines[a]



[a]Reaction conditions were same as those for Table 1, unless otherwise noted.

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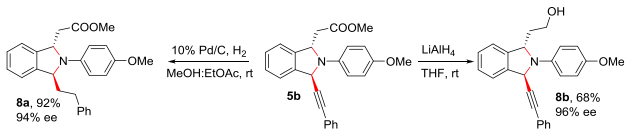
complex catalyzed three-component imination−alkynylation−aza-Michael sequence.

To demonstrate the synthetic utility of the protocol, isoindoline **5b** was transformed into the corresponding alcohol **8b** with a 68% yield and 96% ee by $LiAlH_4$ reduction. Alkyne functionality was easily hydrogenated by molecular hydrogen in the presence of 10% Pd/C to furnish **8a** in 92% yield and 94% ee (Scheme 6).

Scheme 6. Useful Transformations of the Product



In conclusion, we developed a multicomponent reaction sequence for the synthesis of 1,3-disubstituted isoindolines and tetrahydroisoquinolines with an unprecedented level of yield as well as enantio- and diastereoselectivity. Three elementary steps, imination−alkylation−aza-Michael, occur in one pot to furnish the product. Substituted aldehydes were synthesized in one step from the commercially available starting material. The reaction was scaled up to demonstrate the practical usefulness. Transformation of the ester and alkyne functionalities shows the synthetic potential of the methodology. This succinct and flexible methodology offers ample opportunity of its application in complex natural product synthesis, which we are currently working on.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01507.

Experimental procedures, and characterization data and spectra of new compounds (PDF)

Accession Codes

CCDC 1893283 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(24) LHMDS was the best for cyclization among other bases, such as NEt_3, DBU, DABCO, etc. in terms of yield and dr.

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