A highly diastereoselective, catalytic three-component assembly reaction for the synthesis of spiropyrrolidinyloxindoles†

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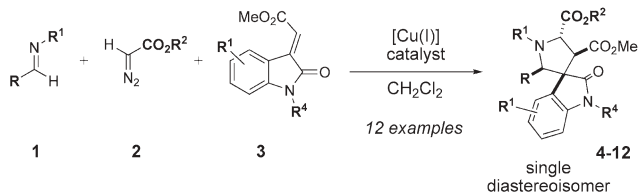
Received (in Bloomington, IN, USA) 28th June 2006, Accepted 18th October 2006
First published as an Advance Article on the web 6th November 2006
DOI: 10.1039/b609155e

Spiropyrrolidinyloxindole compounds are synthesized in moderate to excellent yield *via* a highly diastereoselective Cu(I)-catalysed three-component assembly reaction of an imine, diazo-compound and substituted olefin dipolarophile.



Multi-component coupling reactions (MCCRs) are a powerful method for the rapid generation of complex molecular architectures.[1] MCCRs are particularly useful for the construction of biologically relevant natural products[2] and platforms for diversity-oriented synthesis[3] in a convergent and atom economical manner.[4] The spirooxindole core features in a number of natural products such as (−)-horsfiline,[5] elacomine,[6] alstonisine,[7] strychnofoline[8] and spirotryprostatins A and B,[9] as well as medicinally relevant compounds.[10] Recently, the spiropyrrolidinyl-oxindole core of these molecules has been the subject of significant synthetic interest.[11] In addition to the classical oxidative rearrangement of carbolines,[12] and the intramolecular Mannich reaction between an oxindole and an imine derivative of L-tryptophan,[13] there have been several approaches to this alkaloid core using radical cyclizations.[14] Carreira and co-workers have developed a MgI_2-catalysed ring expansion of a spirocyclopropane-1,3′-oxindole and an aldimine for the synthesis of several related natural products.[15a–c] In 2000, Overman demonstrated the total synthesis of spirotryprostatin B *via* the intramolecular trapping of a π-allyl complex by a oxindole enolate, and more recently a synthesis of (−)-horsfiline was disclosed involving a related palladium-catalysed asymmetric allylic alkylation.[16] Williams reported an elegant asymmetric synthesis of the spirotryprostatins using a chiral azomethine ylide generated from chiral 5,6-diphenylmorpholin-2-one and a substituted aldehyde in four steps,[17] which has provided the synthetic platform for library-based medicinal evaluation of these spiroxindoles and their analogues.[18] Consequently, an efficient non-linear synthetic strategy to access spiropyrrolidinyloxindoles efficiently could advance the understanding of how these compounds interact with biological systems.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds as well as X-ray crystallographic data for **9**. See DOI: 10.1039/b609155e

Here we report a catalytic, multi-component approach employing dipolarophile **3** derived from isatin.[19] We recently published a catalytic three-component assembly reaction for the synthesis of pyrrolidines and dihydropyrroles involving an imine, a diazoester and an unsaturated coupling partner.[20a] In this convergent approach, significant molecular complexity is generated in a single operation from readily available starting materials. The combination of copper(I) and diazo compounds produces the corresponding metallocarbenoid. The presence of an imine during this process generates an azomethine ylide intermediate with the carbon derived from the diazoester *cis* to the benzylidene substituent.

The diastereoselectivity of the cycloaddition was determined by single crystal X-ray diffraction (Fig. 1).[21] In our current understanding of this process, the rate of (*E*)–(*Z*) isomerization of the azomethine ylide generated *in situ* is slower than the rate of the cycloaddition since only 2,5-*trans* stereochemistry of the resulting cycloadduct is observed (Scheme 1).[20a–d] In addition, the dipolarophile alkene geometry is directly translated to the cycloaddition products.[20a] Our model involves an *E-exo* transition state (*E* referring to the imine geometry and *exo* to the relative orientation of the two ester groups—as described by Williams and Sebehar[17]) leading to the observed regio- and diasteroselectivity.

Gratifyingly, each component of the reaction manifold allows for facile diversification. Thus a collection of spiropyrrolidinyl-oxindoles can be readily prepared (Table 1). Substitution on the starting imine is tolerated, especially on the benzylidene aryl ring (compounds **5–7**, entries 2–4), although a *para*-methoxy group

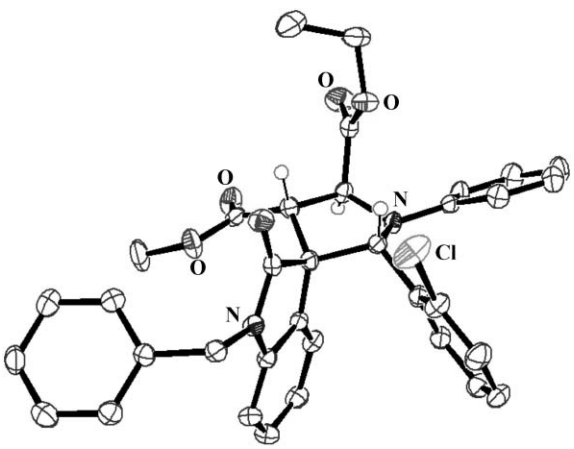
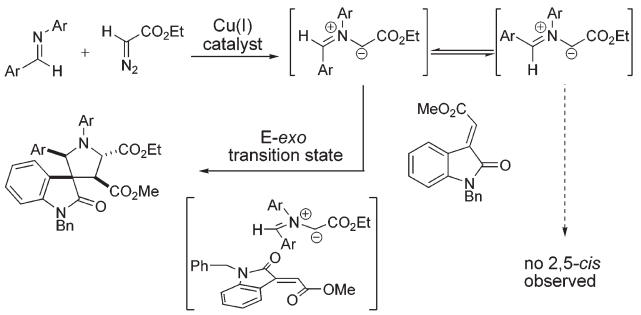


Fig. 1 ORTEP representation of crystal structure of substituted spiropyrrolidinyloxindole **9**. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms other than those in the pyrrolidine ring have been omitted for clarity.

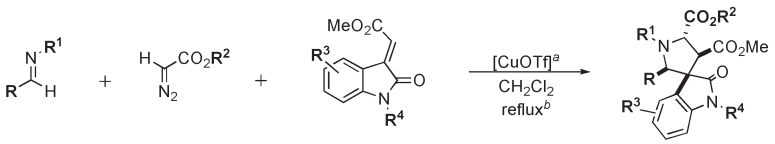


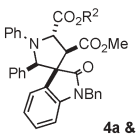
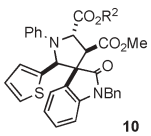
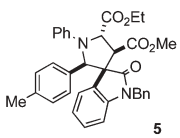
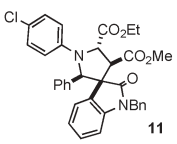
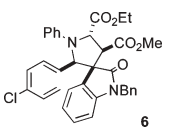
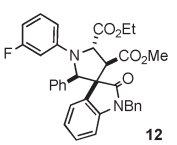
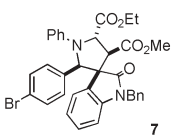
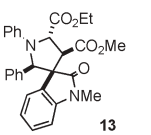
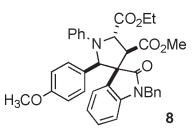
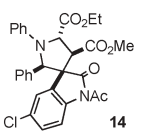
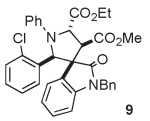
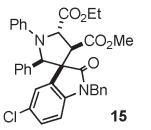
Scheme 1 Mechanistic and stereochemical considerations of the MCCR.

leads to a lower yield (compound **8**, entry 5) and the formation of side products. Even a 2-chlorophenyl (compound **9**, entry 6), and a heterocyclic imine (compound **10**, entry 7), could be employed in the reaction. Substituted aniline imines lead to a decrease in yield of product (compounds **11** and **12**, entries 8 and 9), most likely due to a destabilising effect on the putative azomethine ylide. *tert*-Butyl diazoacetate could be readily substituted in place of EDA, to further differentiate the esters for future synthetic endeavours (entry 1b, 74% yield). Alternative *N*-substituents (methyl and acetate) were introduced at the dipolarophile nitrogen atom (entries 10 and 11). Finally, a substituted dipolarophile undergoes cycloaddition smoothly (20 mol% of catalyst used, 84% yield, entry 12). Of particular note, no carbon–hydrogen insertion is observed at the *N*-benzylic position, although in the event this amide nitrogen is left unprotected, significant nitrogen–hydrogen insertion occurs (*ca.* 30%).

Freshly prepared 10–20 mol% copper(I) trifluoromethane sulfonate dimer benzene complex[22] is the optimal catalyst system, commercial copper(I) trifluoromethane sulfonate dimer–benzene

Table 1 Scope of copper-catalysed MCCR



Entry		Product	Yield (%)[c]	d.r.[d]	Entry		Product	Yield (%)[c]	d.r.[d]
1	R = R^1 = Ph, R^2 = (a) Et, (b) *t*-Bu R^3 = H, R^4 = Bn	 **4a & 4b**	(a) 79 (b) 74	20 : 1	7	R = 2-thiophenyl, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **10**	43[e]	20 : 1
2	R = 4-$CH_3C_6H_4$, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **5**	72	20 : 1	8	R = Ph, R^1 = 4-ClC_6H_4, R^2 = Et, R^3 = H, R^4 = Bn	 **11**	50[e]	20 : 1
3	R = 4-ClC_6H_4, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **6**	60	20 : 1	9	R = Ph, R^1 = 3-FC_6H_4, R^2 = Et, R^3 = H, R^4 = Bn	 **12**	41[f]	20 : 1
4	R = 4-BrC_6H_4, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **7**	55	20 : 1	10	R = R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Me	 **13**	69	20 : 1
5	R = 4-$CH_3OC_6H_4$, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **8**	46[e]	20 : 1	11	R = R^1 = Ph, R^2 = Et, R^3 = 5′Cl, R^4 = Ac	 **14**	56	20 : 1
6	R = 2-ClC_6H_4, R^1 = Ph, R^2 = Et, R^3 = H, R^4 = Bn	 **9**	53	20 : 1	12	R = R^1 = Ph, R^2 = Et, R^3 = 5′Cl, R^4 = Bn	 **15**	84[f]	20 : 1

[a] $(C_6H_6)\cdot[Cu(OTf)]_2$. [b] Reaction conditions: A solution of diazo compound (**2a** or **2b**, 3 equiv.) in CH_2Cl_2 (3 mL) was added *via* syringe pump over 3 h to a refluxing solution of imine (**1a–j**, 3 equiv.) and 10 mol% $(C_6H_6)\cdot[Cu(OTf)]_2$ in CH_2Cl_2 (5 mL). The reaction was heated for a further 1–2 h, the solvent was removed and the residue purified on SiO_2. [c] Isolated yields. [d] Diastereoisomeric ratios were determined by ^1H NMR spectra of unpurified reaction mixtures. Relative stereochemistry of products were assigned based on analogy to the X-ray crystal structure of **9** (Fig. 1). [e] 15 mol% $(C_6H_6)\cdot[Cu(OTf)]_2$/4 equiv. imine. [f] 20 mol% $(C_6H_6)\cdot[Cu(OTf)]_2$/4.5 equiv. imine/6 h syringe pump addition.

complex, copper(I) hexafluorophosphate tetrakisacetonitrile and dirhodium tetraacetate all yield significantly less product.[23] Typically 10 mol% of copper complex is sufficient to produce good yields of product, although in some cases 15–20 mol% of the dimer complex is required to produce synthetically useful yields (entries 5 and 7–9). Despite the lower chemical yields of these entries, this privileged alkaloid structure is accessed from readily available starting materials in a rapid and efficient manner.

In summary, the combination of an α-diazoester and an imine in the presence of a copper(I) catalyst generates a reactive, transient azomethine ylide. This 1,3-dipole undergoes a highly diastereoselective cycloaddition with a dipolarophile to afford a highly-substituted spiropyrrolidinyloxindole heterocycle in a convergent, three-component assembly reaction. Notably, this process is capable of generating four contiguous stereogenic centres in one operation by employing commercially available catalysts. The biological evaluation of these compounds is currently underway.

Support for this research has been provided by the NSF (Career award to K. A. S.), Northwestern University and the Elizabeth Tuckerman Foundation (for a scholarship to C. V. G.). K. A. S. thanks Abbott, Amgen, Boehringer-Ingelheim and 3 M for generous unrestricted research support. J. S. M. thanks Northwestern University for a Summer Undergraduate Research Grant. We thank the Analytical Services Laboratory (ASL) at Northwestern University for assistance with NMR experiments and single crystal X-ray diffraction (C. S.).

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21 Crystallographic data for compound **9**: $C_{35}H_{31}ClN_2O_5$, M = 595.07, monoclinic, space group $P2_1/c$, a = 13.1699(14), b = 16.1972(17), c = 14.1817(14) Å, β = 103.160(2)°, U = 2945.7(5) Å^3, T = 153(2) K, Z = 4, ρ = 1.342 Mg m^{-3}, μ = 0.177 mm^{-1}; Reflections collected/unique 26840/7120 [R_{int} = 0.1034, wR_2 = 0.1033 for all data]. CCDC 612894. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609155e.

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23 The yields for commercial copper(I) trifluoromethane sulfonate dimer–benzene complex, copper(I) hexafluorophosphate tetrakisacetonitrile and dirhodium tetraacetate for compound **4a** are 44%, 36% and 27%, respectively.