



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2015, 6, 6448

Copper-catalyzed condensation of imines and α -diazo- β -dicarbonyl compounds: modular and regiocontrolled synthesis of multisubstituted pyrroles†

Wei Wen Tan and Naohiko Yoshikai*

In the presence of a copper(II) catalyst, enolizable imines bearing various *N*-substituents and α -diazo- β -ketoesters undergo denitrogenative and dehydrative condensation to afford highly substituted pyrroles in moderate to good yields with exclusive regioselectivity. The reaction likely involves nucleophilic addition of the imine nitrogen to a copper carbenoid, tautomerization of the resulting azomethine ylide to an α -enamino ketone, and a subsequent enamine–ketone cyclocondensation. With $\text{Yb}(\text{OTf})_3$ as a unique cocatalyst, α -diazo- β -diketones also participate in the same condensation reaction. The present reaction is applicable to acyclic, exocyclic, and endocyclic imines with tolerance of a broad range of functional groups and heterocyclic moieties, thus opening a new convenient route for the synthesis of the lamellarin family of natural products.

Received 26th June 2015

Accepted 31st July 2015

DOI: 10.1039/c5sc02322j

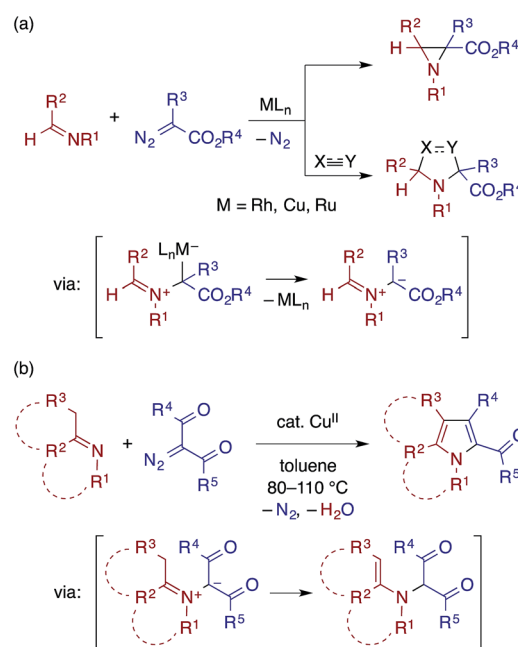
www.rsc.org/chemicalscience

Introduction

Transition metal carbenoids, generated through the decomposition of diazocarbonyl compounds, have been proven to serve as extremely versatile electrophilic intermediates for organic synthesis.¹ Among the various carbenoid transformations, reactions using aldimines bearing *N*-aryl or *N*-alkyl substituents as nucleophilic reaction partners have been extensively explored as they offer useful methods for the synthesis of nitrogen-containing heterocycles (Scheme 1a). In a prototypical reaction pattern, the nucleophilic addition of the aldimine nitrogen atom to the carbenoid gives rise to a metal-bound or a free azomethine ylide.² The azomethine ylide then undergoes intramolecular cyclization to afford an aziridine derivative—a process that can be made enantioselective using a chiral metal catalyst.³ The azomethine ylide can also be intercepted by an appropriate dipolarophile, such as an electron-deficient alkene or alkyne, thus affording a pyrrolidine or related heterocycle through [3 + 2] cycloaddition.^{4,5}

In contrast to the extensive studies on the carbenoid reactions with aldimines, reports on transition metal-catalyzed reactions of ketimines with diazocarbonyl compounds are very rare. While isatin-derived ketimines were reported to react with a rhodium carbenoid derived from diazomalonnate to generate azomethine ylides for [3 + 2] cycloaddition,⁶ in other examples, ketimines do

not directly react with a metal carbenoid but undergo [2 + 2] cycloaddition with a ketene generated through a Wolff rearrangement of the carbenoid.⁷ To our knowledge, reactions of



- Regiocontrolled access to highly substituted pyrroles
- Broad scope of imines and diazodicarbonyl compounds
- Applicable to Lamellarin synthesis

Scheme 1 Transition metal-catalyzed condensation of imines and diazocarbonyl compounds.

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: nyoshikai@ntu.edu.sg

† Electronic supplementary information (ESI) available: CCDC 1040843 and 1063222. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc02322j



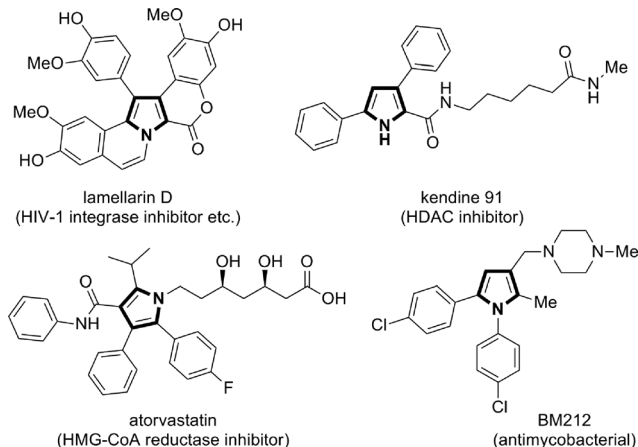


Chart 1 Examples of pyrrole-containing bioactive molecules.

other types of ketimines, including those bearing α -protons, with metal carbenoids have not been documented in the literature. In pursuit of heterocycle synthesis through the transition metal catalysis of ketimines,⁸ we have found that a ketimine derived from an enolizable ketone participates in the reaction with an α -diazo- β -ketoester (or diketone) under copper catalysis to afford a multisubstituted pyrrole with the concomitant loss of dinitrogen and water (Scheme 1b), which is reported herein. The reaction is considered to involve the nucleophilic addition of the ketimine nitrogen to a copper carbenoid and the tautomerization of the resulting azomethine ylide to an α -enamino- β -dicarbonyl intermediate, which then undergoes dehydrative cyclocondensation to give the pyrrole product. The reaction is applicable to ketimines with various skeletons and *N*-substituents, and features a simple catalytic system and operation.

Multisubstituted pyrroles are present in many natural products, pharmaceutically relevant compounds, and other functional molecules (Chart 1).⁹ While a number of new synthetic methods for multisubstituted pyrroles, those catalyzed by transition metals in particular, have been developed in the last decades,^{10,11} the demand for simple, robust, and sustainable methods remains high. Notably, in many of the recent transition metal-catalyzed methods, the catalyst plays a key role in the formation of linear intermediates such as α -enamino-ketone,¹² γ -ketoimine (or its tautomers),¹³ and 1,4-diimine,¹⁴ which undergo dehydrative or deaminative cyclocondensation to afford the pyrrole products. In this context, the present reaction represents a useful addition to the synthetic repertoire for pyrroles, because the substitution patterns of the key α -enamino- β -dicarbonyl intermediates are otherwise not readily accessible.¹⁵ As such, the present reaction enables the modular and expeditious preparation of dozens of new multisubstituted pyrroles and also opens a new alternative route for the synthesis of the lamellarin family of natural products.

Results and discussion

The present study commenced with attempts on the condensation of imine **1a**, derived from acetophenone and *p*-anisidine, with α -

diazo- β -ketoester **2a**, derived from ethyl isobutyrylacetate (Table 1). Upon the screening of various reaction conditions, the desired condensation was found to proceed efficiently in the presence of catalytic copper(II) trifluoroacetylacetonate ($\text{Cu}(\text{tfacac})_2$, 10 mol%) and 4 Å molecular sieves (MS) in toluene at 110 °C to afford the tetrasubstituted pyrrole **3aa** as the exclusive regioisomer in 88% yield (entry 1). The regiochemistry of **3aa** was confirmed by two-dimensional NMR (HMQC and HMBC) analysis. While copper(II) hexafluoroacetylacetonate ($\text{Cu}(\text{hfacac})_2$) showed a comparable catalytic activity to $\text{Cu}(\text{tfacac})_2$ (entry 2), other copper salts such as $\text{Cu}(\text{acac})_2$ and $\text{Cu}(\text{OAc})_2$ were much less effective (entries 3 and 4). The use of $\text{Rh}_2(\text{OAc})_4$ resulted in the formation of an intractable mixture of products, in which the desired product **3aa** was not detected (entry 5). The yield of **3aa** diminished substantially in the absence of the 4 Å MS (entry 6). The reduction of the catalyst loading (to 5 mol%) or the reaction temperature (to 90 °C) resulted in slightly lower yields (entries 7 and 8). 1,2-Dichloroethane (DCE) can be used as an alternative solvent (entry 9), while the reaction was completely shut down in DMSO (entry 10). Note that the formation of an aziridine product was not observed during the optimization study.^{3a-e}

To explore the scope of the present pyrrole synthesis, we first subjected various *N*-PMP ketimines **1a–1u** to the reaction with the diazoester **2a** (Table 2). The imines **1a–1o** derived from a wide variety of (hetero)aryl methyl ketones could be condensed with **2a**, affording the tetrasubstituted pyrroles **3aa–3oa** in moderate to good yields. The X-ray diffraction analysis of single crystals of **3ja** unambiguously confirmed its regiochemistry. The reaction of the parent acetophenone imine **1a** could be performed on a gram (5 mmol) scale without problem (see **3aa**). Various functional groups, such as halogen (F, Cl, Br, I), trifluoromethyl, cyano, and nitro groups, as well as heteroaryl

Table 1 Screening of the reaction conditions^a

Entry	Deviation from the standard conditions	Yield ^b (%)
1	None	88 ^c
2	$\text{Cu}(\text{hfacac})_2$ instead of $\text{Cu}(\text{tfacac})_2$	87
3	$\text{Cu}(\text{acac})_2$ instead of $\text{Cu}(\text{tfacac})_2$	7
4	$\text{Cu}(\text{OAc})_2$ instead of $\text{Cu}(\text{tfacac})_2$	21
5	$\text{Rh}_2(\text{OAc})_4$ instead of $\text{Cu}(\text{tfacac})_2$	0
6	Without 4 Å MS	52
7	5 mol% of $\text{Cu}(\text{tfacac})_2$	76
8	$T = 90$ °C	82
9	DCE instead of toluene	81
10	DMSO instead of toluene	0

^a The reaction was performed using 0.2 mmol of **1a** and 0.3 mmol of **2a**. PMP = *p*-methoxyphenyl. $\text{Cu}(\text{tfacac})_2$ = copper(II) trifluoroacetylacetonate. $\text{Cu}(\text{hfacac})_2$ = copper(II) hexafluoroacetylacetonate. ^b Determined by GC. ^c Isolated yield.



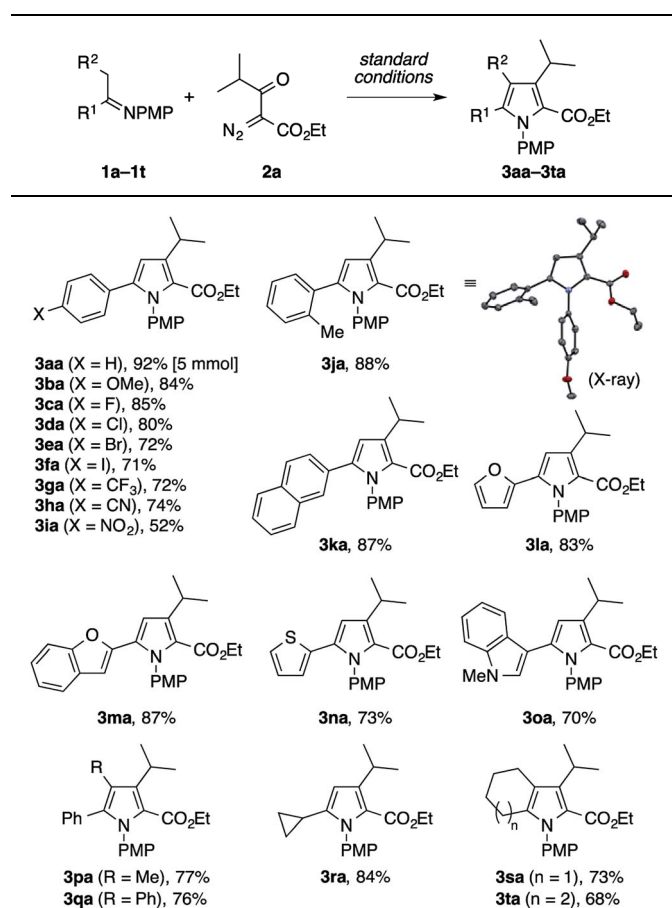
moieties such as furyl, benzofuryl, thienyl, and indolyl groups, were tolerated. The imines **1p–1t** derived from propiophenone, 2-phenylacetophenone, cyclopropyl methyl ketone, and cycloalkanones also participated in the reaction with **2a** to afford the corresponding penta- or tetrasubstituted pyrroles **3pa–3ta** in moderate to good yields.

The present condensation reaction is applicable to imines bearing *N*-substituents other than the PMP group, as illustrated in Table 3. The reaction of the acetophenone imine bearing the *N*-4-chlorophenyl group (**1u**) with **2a** afforded the desired product **3ua** in 42% yield, which was markedly lower than that obtained with the *N*-PMP imine **1a**. This suggests the relevance of the electron-richness of the nitrogen atom to the reactivity of the imine. The imines **1v–1z** bearing removable benzyl, 4-methoxybenzyl (PMB), and allyl groups smoothly participated in the reaction with **2a** to afford the pyrroles **3va–3za** in respectable yields of 57–73%, thus making the preparation of *N*-H pyrroles feasible. For example, the removal of the PMB group of **3ya** was achieved in 90% yield with the aid of trifluoroacetic acid and anisole. The methyl-substituted dihydroisoquinoline **1aa**, readily prepared by the Bischler–Napieralski reaction, was also

amenable to the condensation with **2a** to afford a 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivative **3aaa**, implying the potential applicability of the present method to the synthesis of the lamellarin family of natural products (*vide infra*).^{9b–c} Interestingly, the benzyl-substituted dihydroisoquinoline **1ab** afforded a mixture of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **3aba** and an unexpected dihydrobenz[*g*]indolizinone derivative **3aba'**.¹⁶ The latter product features the migration of the phenyl group of **1ab** from the β -position of the nitrogen atom to the α -position, as well as the concomitant oxidation of the β -position. We consider that these structural changes occur on the reaction pathway leading to the pyrrole product **3aba**, rather than after the formation of **3aba**, because the ratio of **3aba** and **3aba'** was not affected by the reaction time (see Scheme S1 in the ESI† for a possible mechanism).

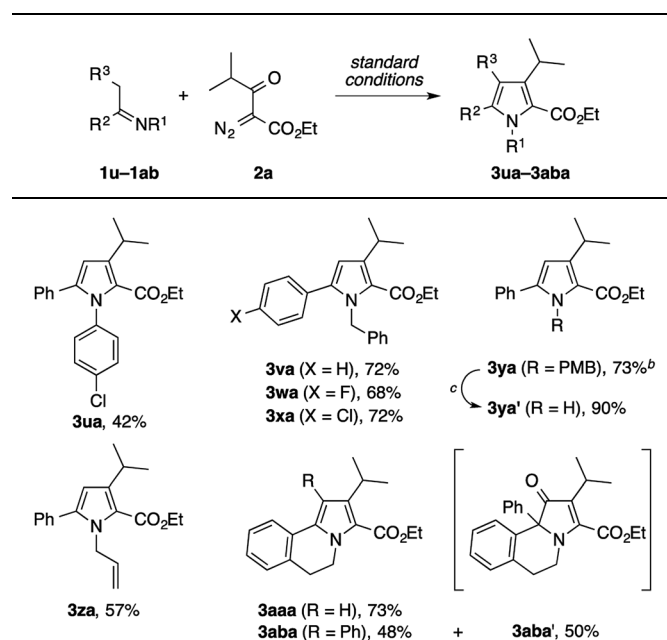
Besides the isolable imines described above, we also examined the viability of unstable imines as reactants for the present pyrrole synthesis (Scheme 2). First, an *N*-H imine of acetophenone **1ac**, prepared from benzonitrile and methyl lithium with minimal workup, was subjected to the reaction with ethyl acetyldiazoacetate **2b**, which afforded the desired *N*-H pyrrole **3acb** in a modest yield (Scheme 4a). Interestingly, the reaction was accompanied by the formation of a 2*H*-1,4-oxazine derivative **4** as a byproduct. Next, the condensation of 4-methoxyphenylacetaldehyde and *p*-anisidine and the subsequent reaction of the resulting aldimine **1ad** and **2b** were performed in a one-pot manner. Although the first condensation step was inevitably complicated by side reactions such as the enamine aldol reaction, the desired tetrasubstituted pyrrole **3adb** was obtained in a modest yield (Scheme 4b).

Table 2 Condensation of various *N*-PMP imines with diazoketoester **2a**^a



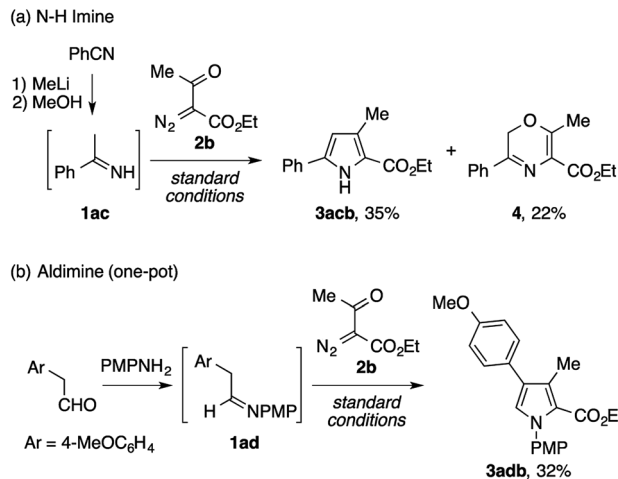
^a The reaction was performed on a 0.2 mmol scale according to the standard conditions described in Table 1.

Table 3 Condensation of other imines with diazoketoester **2a**^a



^a The reaction was performed on a 0.2 mmol scale according to the standard conditions described in Table 1. ^b Performed on a 0.5 mmol scale. ^c TFA, anisole, CH₂Cl₂, 37 °C, 40 h.



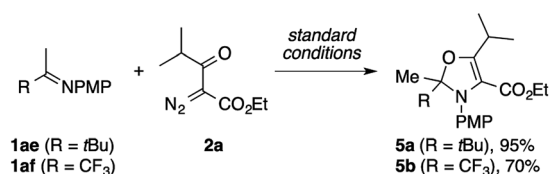


Scheme 2 Condensation of unstable imines with diazoketone 2b.

During the exploration of the scope of the imines, we encountered a few cases of an unexpected mode of cyclization (Scheme 3). The reaction of the pinacolone-derived imine **1ac** with **2a** cleanly furnished a 2,3-dihydrooxazole derivative **5a**, rather than the expected pyrrole. The same reaction was also observed using the trifluoroacetone-derived imine **1af**.

We next explored the reaction of imine **1a** with various α -diazo- β -ketoesters **2b–2p** (Table 4). The reaction allowed the facile preparation of tetrasubstituted pyrroles bearing alkyl (entries 1–3), benzyl (entry 4), and (hetero)aryl (entries 5–12) groups in moderate to good yields, with tolerance of functional groups such as bromo and nitro groups (entries 7, 8, and 10). Diazoketone derived from diethyl 2-oxosuccinate and ethyl 4,4,4-trifluoroacetate could also be condensed with **1a**, thus furnishing 2,3-diethoxycarbonylpyrrole **3an** and 2-ethoxycarbonyl-3-trifluoromethylpyrrole **3ao**, respectively (entries 13 and 14). In addition to the 1,2,3,5-tetrasubstituted pyrroles **3ab–3ao**, the 1,2,5-trisubstituted pyrrole **3ap** was also successfully prepared in a moderate yield using ethyl formyl diazoacetate **2p** as the reactant (entry 15).

The reaction of **1a** with 3-diazopentane-2,4-dione **2q** under the standard conditions with $\text{Cu}(\text{tfacac})_2$ did not give the desired pyrrole product. The use of $\text{Cu}(\text{hfacac})_2$ instead of $\text{Cu}(\text{tfacac})_2$ promoted the reaction, but produced a *ca.* 1 : 1 mixture of the expected pyrrole **3aq** and its positional isomer **3aq'** in a low overall yield (Scheme 4a). The latter isomer would be formed through the formal C–H insertion of a copper carbenoid into the α -position of **1a**. Interestingly, the efficiency and the chemoselectivity of this reaction were substantially



Scheme 3 Formation of dihydrooxazole derivatives.

Table 4 Condensation of the imine **1a** with various α -diazo- β -ketoesters^a

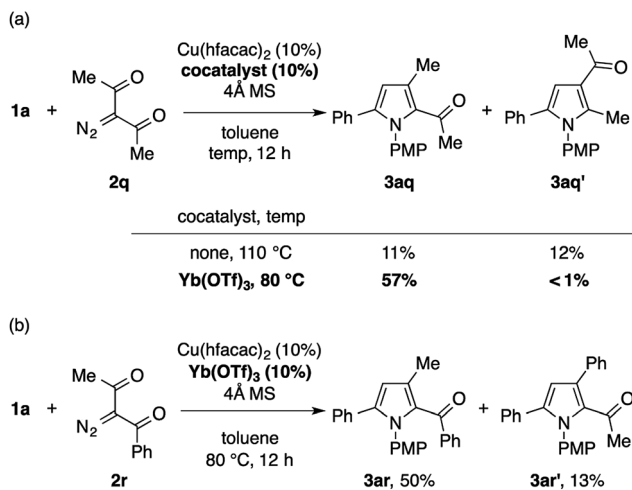
Entry	R ¹	R ²	Product	Yield (%)
1	Me	Et	3ab	81
2	<i>c</i> -C ₃ H ₅	Et	3ac	80
3	<i>c</i> -C ₆ H ₁₁	Me	3ad	88
4	Bn	Me	3ae	94
5	Ph	Et	3af	77
6	4-MeOC ₆ H ₄	Et	3ag	77
7	4-BrC ₆ H ₄	Et	3ah	86
8	4-NO ₂ C ₆ H ₄	Et	3ai	80
9	2-MeC ₆ H ₄	Et	3aj	67
10	2-BrC ₆ H ₄	Et	3ak	60
11	1-Naphthyl	Me	3al	74
12	2-Furyl	Me	3am	70
13	CO ₂ Et	Et	3an	79
14	CF ₃	Et	3ao	41
15	H	Et	3ap	47

^a The reaction was performed on a 0.2 mmol scale according to the standard conditions described in Table 1.

improved by adding $\text{Yb}(\text{OTf})_3$ (10 mol%) and lowering the temperature to 80 °C.¹⁷ Thus, the 2-acetylpyrrole isomer **3aq** was obtained almost exclusively in a respectable yield of 57%. The Cu/Yb cocatalytic system also effected the condensation of **1a** with 1-diazo-1-benzoylacetone **2r** in the same mode of cyclization, in favor of the 2-benzoylpyrrole isomer **3ar** over the 2-acetylpyrrole isomer **3ar'** (Scheme 4b). Note that the same reaction in the absence of $\text{Yb}(\text{OTf})_3$ produced a mixture of four isomers, including **3ar** and **3ar'** in a low overall yield, as suggested by the GC analysis of the crude product. While the role of $\text{Yb}(\text{OTf})_3$ is not clear, we speculate that it serves as a Lewis acid to the diketo moiety to enhance the electrophilicity of the copper carbenoid. Note that the α -diazoketones, such as 2-diazo-1,2-diphenylethanone, decomposed too quickly not only under the standard conditions, but also under conditions employing the less reactive $\text{Cu}(\text{acac})_2$ at a lower temperature, hence producing none of the desired pyrrole product.

Having established the scope and limitation with respect to imines and diazo compounds, we became interested in the applicability of the present condensation reaction to the synthesis of bioactive natural or unnatural products. In this connection, the successful reactions of the dihydroisoquinolines **1aa** and **1ab** (Table 3) turned our attention to the lamellarin family of natural products, many members of which contain a (5,6-dihydro)pyrrolo[2,1-*a*]isoquinoline skeleton. Since the early studies of Steglich, Ishibashi/Iwao, and Banwell,¹⁸ lamellarins have been popular synthetic targets due to the broad spectrum of their biological activities, and have also served as touchstones for new methods for the construction and



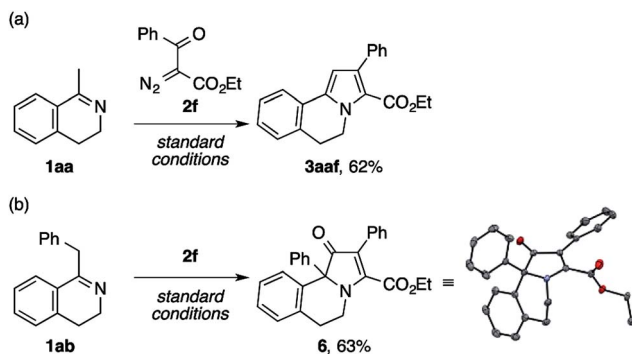


Scheme 4 Condensation of **1a** with α -diazo- β -diketones using a Yb(OTf)₃ cocatalyst.

the functionalization of pyrrole rings.^{9b-c,19} As some of the completed lamellarin syntheses involve 3-alkoxycarbonyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives as key intermediates, we wondered whether the present reaction offers an alternative and efficient route to such intermediates.

Aiming at a straightforward access to the polyarylated pyrrole structure of lamellarins, we first tested model reactions of methyl- and benzylidihydroisoquinolines **1aa** and **1ab** with ethyl benzoyldiazoacetate **2f** (Scheme 5). The reaction of the former imine successfully furnished the desired pyrrole scaffold **3aaf** in 62% yield (Scheme 5a). By contrast, the latter exclusively afforded a dihydrobenz[*g*]indolizone derivative **6**,¹⁶ the structure of which was unambiguously confirmed by X-ray crystallographic analysis (Scheme 5b).

While the above results suggest that the present method may not be suitable for the direct assembly of the pentasubstituted pyrrole core of lamellarins, attempts using ethyl formyldiazoacetate **2p** have proven its utility in the preparation of building blocks for the modular synthesis of lamellarins (Scheme 6). The reaction of methylidihydroisoquinoline with two methoxy groups (**1ag**) and **2p** cleanly afforded the 3-ethoxycarbonyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivative

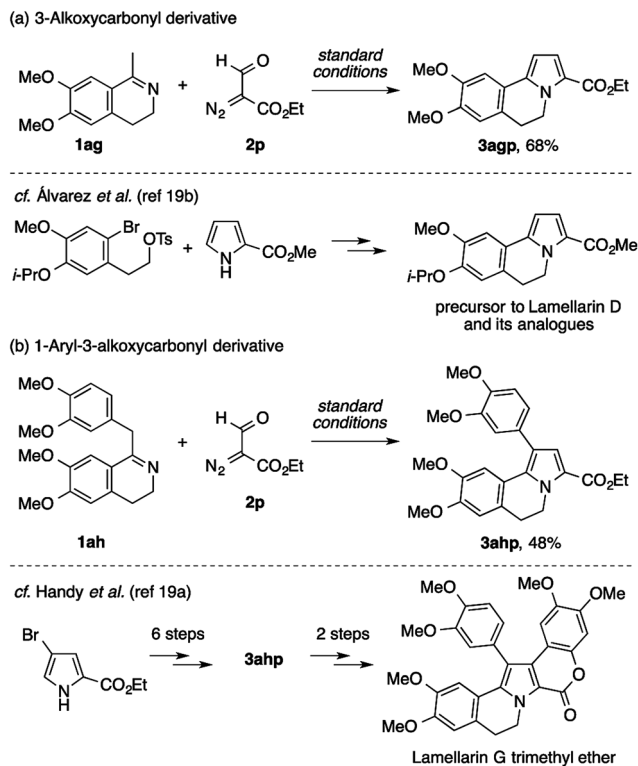


Scheme 5 Model reactions of the dihydroisoquinolines **1aa** and **1ab** with ethyl benzoyldiazoacetate **2f**.

3agp (Scheme 6a). An analogous compound of **3agp** was previously synthesized through a sequence of pyrrole *N*-alkylation and an intramolecular Heck reaction, and used as an intermediate to lamellarin D and its analogues.^{19b,20} Furthermore, benzylidihydroisoquinoline bearing four methoxy groups (**1ah**) also underwent condensation with **2p** to afford the 1-aryl-3-ethoxycarbonyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivative **3ahp** (Scheme 6b). In a previous study by Handy *et al.*, **3ahp** was prepared through the six-step manipulation of a pyrrole-based starting material, and was then converted to lamellarin G trimethyl ether in two steps.^{19a}

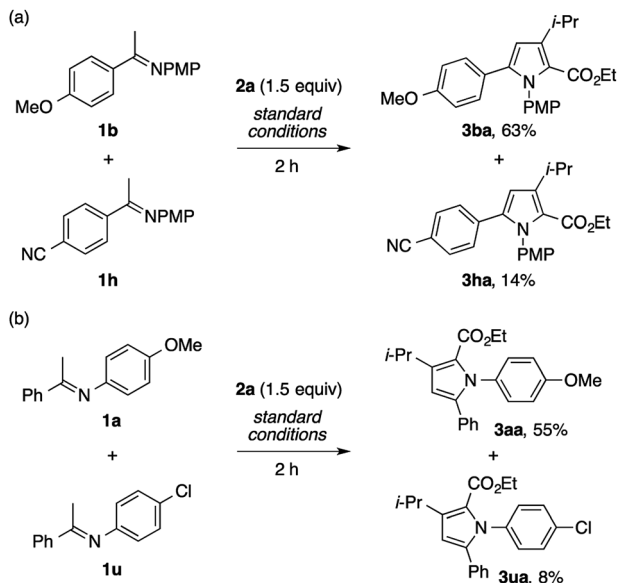
On the basis of the regiochemistry of the pyrrole products as well as common reaction patterns in the transition metal catalysis of diazo compounds, the present reaction is considered to involve the addition of the imine nitrogen to a copper carbenoid.^{2,3,4g} To probe the nature of this putative step, competition experiments using imines bearing different substituents were performed. The reaction of a mixture of the imines **1b** and **1h**, derived from electron-rich and electron-poor acetophenones, respectively, with **2a** afforded the product of the former (**3ba**) as the dominant product (Scheme 7a). Likewise, the reaction of a mixture of the imines **1a** and **1u**, derived from electron-rich and electron-poor anilines, respectively, preferentially produced the product of the former (Scheme 7b). Thus, the nucleophilicity of the imine nitrogen atom would play a critical role in its reaction with the copper carbenoid.

Scheme 8 shows plausible reaction pathways of the present pyrrole synthesis. The decomposition of the diazo compound



Scheme 6 Construction of the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline scaffolds for lamellarin synthesis.





Scheme 7 Competition experiments.

2 with the copper catalyst generates an electrophilic copper carbenoid. Nucleophilic attack of the imine 1 to the carbenoid gives azomethine ylide I^{2-6} and regenerates the copper catalyst. The tautomerization of **I** to α -enamino ketone **II** via proton transfer is followed by cyclocondensation to afford the pyrrole product **3**. Attempts to intercept the azomethine ylide **I** with typical dipolarophiles such as dimethyl acetylenedicarboxylate, dimethyl maleate, and *N*-phenylphthalimide failed to give the corresponding [3 + 2] cycloadducts, but exclusively afforded the pyrrole product, presumably because of the rapid tautomerization of **I** to **II**. Nevertheless, the intermediacy of **I** and **II** rationalizes not only the formation of the pyrrole **3**, but also the side reactions observed in the

present study. In the reaction of the *N*-H imine (Scheme 2), the intermediate **II** may be oxidized to the 1-acyl-2-azadiene **III**, which would then undergo a 6π electrocyclic cyclization to afford a 2*H*-1,4-oxazine derivative **4**.²¹ The azomethine ylide **I** may also behave as an enolate/iminium bifunctional species **I'**, which undergoes an intramolecular attack of the enolate oxygen to the iminium moiety to afford the 2,3-dihydrooxazole **5**. This side reaction would be operative in the cases shown in Scheme 3, possibly because of the lower acidity of the α -proton of the iminium moiety (for **1ae**) or the increased electrophilicity of the iminium moiety (for **1af**).

Conclusions

In conclusion, we have developed a copper-catalyzed condensation reaction of imines and α -diazo- β -dicarbonyl compounds to afford multisubstituted pyrroles in a regiocontrolled manner. The reaction features a broad scope and the ready availability of starting materials and a simple operation, thus enabling the modular and quick preparation of a variety of densely functionalized pyrroles. Given the extensive previous studies on carbenoid reactions with imines,²⁻⁶ it is rather surprising that the present condensation of enolizable imines has not been documented. The reaction opens concise preparative routes to lamellarin scaffolds, and may find further applications in the synthesis of pyrrole alkaloids. The cooperative effect of the carbene transfer catalyst ($\text{Cu}(\text{hfacac})_2$) and the Lewis acid catalyst ($\text{Yb}(\text{OTf})_3$), observed in the reaction of α -diazo- β -diketones, also deserves mechanistic and synthetic explorations. Further studies on heterocycle synthesis using imines as starting materials⁸ and/or based on carbenoid chemistry are currently in progress in our laboratory.

Acknowledgements

This work was supported by the Singapore National Research Foundation (NRF-RF2009-05) and Nanyang Technological University. We thank Dr Malleswara Rao Kuram for his early study and Drs Yongxin Li and Rakesh Ganguly for assistance with the X-ray crystallographic analysis.

Notes and references

- (a) T. Ye and M. A. Mckerverey, *Chem. Rev.*, 1994, **94**, 1091; (b) M. P. Doyle, M. A. Mckerverey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, 1998; (c) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (d) Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577.
- (a) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263; (b) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223.
- (a) K. G. Rasmussen and K. A. Jørgensen, *J. Chem. Soc., Chem. Commun.*, 1995, 1401; (b) K. B. Hansen, N. S. Finney and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1995, **34**, 676; (c) M. Moran, G. Bernardinelli and P. Müller, *Helv. Chim. Acta*, 1995, **78**, 2048; (d) Y. Li, P. W. H. Chan, N.-Y. Zhu,

Scheme 8 Plausible reaction pathways leading to pyrrole and other byproducts.



- C.-M. Che and H.-L. Kwong, *Organometallics*, 2004, **23**, 54; (e) X.-J. Zhang, M. Yan and D. Huang, *Org. Biomol. Chem.*, 2009, **7**, 187; (f) M. P. Doyle, W. H. Hu and D. J. Timmons, *Org. Lett.*, 2001, **3**, 933.
- 4 (a) A. Padwa, D. C. Dean, M. H. Osterhout, L. Precedo and M. A. Semones, *J. Org. Chem.*, 1994, **59**, 5347; (b) G.-Y. Li, J. Chen, W.-Y. Yu, W. Hong and C.-M. Che, *Org. Lett.*, 2003, **5**, 2153; (c) H.-W. Xu, G.-Y. Li, M.-K. Wong and C.-M. Che, *Org. Lett.*, 2005, **7**, 5349; (d) M.-Z. Wang, H.-W. Xu, Y. Liu, M.-K. Wong and C.-M. Che, *Adv. Synth. Catal.*, 2006, **348**, 2391; (e) C. V. Galliford and K. A. Scheidt, *J. Org. Chem.*, 2007, **72**, 1811; (f) C. V. Galliford, J. S. Martenson, C. Stern and K. A. Scheidt, *Chem. Commun.*, 2007, 631; (g) A. P. Kadina, A. F. Khlebnikov, M. S. Novikov, P. J. Perez and D. S. Yufit, *Org. Biomol. Chem.*, 2012, **10**, 5582.
- 5 M. Yan, N. Jacobsen, W. Hu, L. S. Gronenberg, M. P. Doyle, J. T. Colyer and D. Bykowski, *Angew. Chem., Int. Ed.*, 2004, **43**, 6713.
- 6 T. Rajasekaran, G. Karthik, B. Sridhar and B. V. S. Reddy, *Org. Lett.*, 2013, **15**, 1512.
- 7 (a) B. V. S. Reddy, G. Karthik, T. Rajasekaran, A. Antony and B. Sridhar, *Tetrahedron Lett.*, 2012, **53**, 2396; (b) M. D. Mandler, P. M. Truong, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2014, **16**, 740.
- 8 (a) Y. Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.*, 2012, **134**, 9098; (b) Z. Chen, B. Lu, Z. Ding, K. Gao and N. Yoshikai, *Org. Lett.*, 2013, **15**, 1966; (c) B. Lu, J. Wu and N. Yoshikai, *J. Am. Chem. Soc.*, 2014, **136**, 11598; (d) T. Yamakawa and N. Yoshikai, *Org. Lett.*, 2013, **15**, 196.
- 9 (a) M. d'Ischia, A. Napolitano and A. Pezzella, in *Comprehensive Heterocyclic Chemistry III*, Elsevier, Oxford, 2008, pp. 353–388; (b) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264; (c) T. Fukuda, F. Ishibashi and M. Iwao, *Heterocycles*, 2011, **83**, 491; (d) M. Biava, G. C. Porretta and F. Manetti, *Mini-Rev. Med. Chem.*, 2007, **7**, 65; (e) D. Otaegui, A. Rodríguez-Gascón, A. Zubia, F. P. Cossio and J. L. Pedraz, *Cancer Chemother. Pharmacol.*, 2009, **64**, 153; (f) I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801; (g) A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami and H. M. L. Davies, *J. Am. Chem. Soc.*, 2015, **137**, 644.
- 10 (a) J. Bergman and T. Janosik, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, pp. 269–351; (b) V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (c) V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2014, **43**, 4633; (d) F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213; (e) C. Schmuck and D. Rupprecht, *Synthesis*, 2007, 3095.
- 11 (a) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084; (b) N. Yoshikai and Y. Wei, *Asian J. Org. Chem.*, 2013, **2**, 466; (c) N. T. Patil and Y. Yamamoto, *ARKIVOC*, 2007, 121; (d) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127.
- 12 (a) Y. Aoyagi, T. Mizusaki, M. Shishikura, T. Komine, T. Yoshinaga, H. Inaba, A. Ohta and K. Takeya, *Tetrahedron*, 2006, **62**, 8533; (b) S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140; (c) M. Zhang, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 597; (d) M. Zhang, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384; (e) D. Srimani, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 4012; (f) X. Li, M. Chen, X. Xie, N. Sun, S. Li and Y. Liu, *Org. Lett.*, 2015, **17**, 2984.
- 13 (a) H. Takaya, S. Kojima and S.-i. Murahashi, *Org. Lett.*, 2001, **3**, 421; (b) S. Chiba, Y.-F. Wang, G. Lapointe and K. Narasaka, *Org. Lett.*, 2008, **10**, 313; (c) Y.-F. Wang, K. K. Toh, S. Chiba and K. Narasaka, *Org. Lett.*, 2008, **10**, 5019; (d) S. Chiba, Y.-J. Xu and Y.-F. Wang, *J. Am. Chem. Soc.*, 2009, **131**, 12886; (e) H.-Y. Wang, D. S. Mueller, R. M. Sachwani, H. N. Londino and L. L. Anderson, *Org. Lett.*, 2010, **12**, 2290; (f) T. J. Donohoe, N. J. Race, J. F. Bower and C. K. A. Callens, *Org. Lett.*, 2010, **12**, 4094; (g) H.-Y. Wang, D. S. Mueller, R. M. Sachwani, R. Kapadia, H. N. Londino and L. L. Anderson, *J. Org. Chem.*, 2011, **76**, 3203; (h) S. Shafi, M. Kedziorek and K. Grela, *Synlett*, 2011, 124; (i) K. Iida, T. Miura, J. Ando and S. Saito, *Org. Lett.*, 2013, **15**, 1436.
- 14 (a) M. R. Rivero and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 973; (b) D. Ciez, *Org. Lett.*, 2009, **11**, 4282; (c) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin and Y. Jia, *Org. Lett.*, 2010, **12**, 4066.
- 15 (a) X. Qi, X. Xu and C.-M. Park, *Chem. Commun.*, 2012, **48**, 3996; (b) D. Hong, Y. Zhu, Y. Li, X. Lin, P. Lu and Y. Wang, *Org. Lett.*, 2011, **13**, 4668; (c) X. Xu, M. O. Ratnikov, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2011, **13**, 6122; (d) E. Lourdusamy, L. Yao and C.-M. Park, *Angew. Chem., Int. Ed.*, 2010, **49**, 7963; (e) C. Dong, G. Deng and J. Wang, *J. Org. Chem.*, 2006, **71**, 5560; (f) M. N. Eberlin and C. Kascheres, *J. Org. Chem.*, 1988, **53**, 2084.
- 16 (a) S. T. Heller, T. Kiho, A. R. H. Narayan and R. Sarpong, *Angew. Chem., Int. Ed.*, 2013, **52**, 11129; (b) H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1988, 869; (c) T. Eicher and D. Krause, *Synthesis*, 1986, 899.
- 17 Other metal triflates also changed the regioselectivity in favor of the product **3aq**. See the ESI† for details.
- 18 (a) A. Heim, A. Terpin and W. Steglich, *Angew. Chem., Int. Ed.*, 1997, **36**, 155; (b) F. Ishibashi, Y. Miyazaki and M. Iwao, *Tetrahedron*, 1997, **53**, 5951; (c) M. Banwell, B. Flynn and D. Hockless, *Chem. Commun.*, 1997, 2259.
- 19 (a) S. T. Handy, Y. N. Zhang and H. Bregman, *J. Org. Chem.*, 2004, **69**, 2362; (b) D. Pla, A. Marchal, C. A. Olsen, F. Albericio and M. Alvarez, *J. Org. Chem.*, 2005, **70**, 8231; (c) P. Ploypradith, T. Petchmanee, P. Sahakitpichan, N. D. Litvinas and S. Ruchirawat, *J. Org. Chem.*, 2006, **71**, 9440; (d) J. T. Gupton, E. J. Banner, M. D. Sartin, M. B. Coppock, J. E. Hempel, A. Kharlamova, D. C. Fisher, B. C. Giglio, K. L. Smith, M. J. Keough, T. M. Smith, R. P. F. Kanters, R. N. Dominey and J. A. Sikorski, *Tetrahedron*, 2008, **64**, 5246; (e) Q. Li, J. Jiang, A. Fan, Y. Cui and Y. Jia, *Org. Lett.*, 2011, **13**, 312; (f) K. Hasse, A. C. Willis and M. G. Banwell, *Eur. J. Org. Chem.*, 2011, 88; (g) D. Imbri, J. Tauber and T. Opatz, *Chem.-Eur. J.*, 2013, **19**, 15080; (h) M. Komatsubara, T. Umeki, T. Fukuda and



- M. Iwao, *J. Org. Chem.*, 2014, **79**, 529; (i) K. Ueda, K. Amaike, R. M. Maceiczky, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 13226.
- 20 D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio and M. Alvarez, *J. Med. Chem.*, 2006, **49**, 3257.
- 21 V. A. Khlebnikov, M. S. Novikov, A. F. Khlebnikov and N. V. Rostovskii, *Tetrahedron Lett.*, 2009, **50**, 6509.

