Oxygen Heterocycles

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Diastereoselective Synthesis of Cyclopenta[*c*]furans by a Catalytic Multicomponent Reaction

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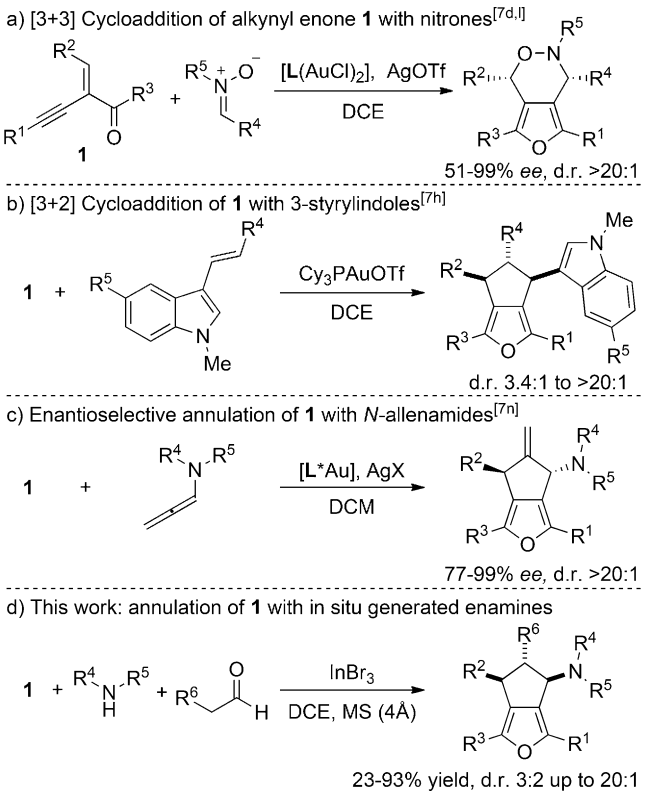
Abstract: *A diastereoselective three-component reaction between alkynyl enones, aldehydes and secondary amines is reported. With the aid of a benign indium catalyst, a range of highly substituted cyclopenta[c]furan derivatives can be obtained in a single-step procedure. The formation of the stereodefined heterocyclic motifs takes place via in situ generation of enamines followed by two sequential cyclization steps.*

Multicomponent reactions (MCRs) involving sequential cyclization steps are powerful approaches for the construction of structurally diverse scaffolds of chemical and biological interest.[1] The selective formation of multiple bonds in a single operational step offers a challenge as well as a great potential for improving atom economy, step efficiency and sustainability in synthesis. Ideally, multicomponent reactions do not only allow for modulative syntheses of compounds with divergent substitution patterns, but may also provide a platform for further transformations.

An example of valuable heterocyclic motifs where MCR approaches have been utilized is furan derivatives.[2] These motifs are important in organic synthesis due to their presence as key structural scaffolds in certain natural products and pharmaceuticals,[3] and also as useful building blocks for synthesis.[4]

Transition metal catalysis has been widely used as a tool for the synthesis of functionalized furan derivatives.[5] The use of gold catalysis for the cyclization of 2-(1-alkynyl)-2-alken-1-ones was first reported by Larock[6] in 2004 and has since been further developed by Zhang[7] and others.[8] For example, the Au^I-catalyzed intermolecular reactions of alkynyl enones with nitrones,[7d,l] 3-styrylindoles,[7h] and *N*-allenamides[7n] provide access to highly functionalized furans (Scheme 1 a–c).



Scheme 1. Applications of alkynyl enones for furan synthesis.

Despite the success of transition metal catalysis for the assembly of valuable heterocycles via π-Lewis acid activation, the use of p-block elements can offer new synthetic possibilities. As previously demonstrated, indium reagents and catalysts generally display a high functional group tolerance, providing a useful tool for novel transformations.[9] Herein, a catalytic MCR of alkynyl enones **1**, aldehydes and secondary amines is reported (Scheme 1 d).

In order to develop an efficient catalytic system, and to avoid the formation of hydroamination and aza-Michael side-products, a catalyst screening using alkynyl enone **1a**, hydrocinnamaldehyde (**2a**), and diisopropylamine (**3a**) was performed (Table 1). In analogy with literature reports, we investigated PPh_3AuCl as a catalyst in the presence of molecular sieves in 1,2-dichloroethane (Table 1, entries 1–3). In the absence of Ag^I salts, no formation of cyclopenta[*c*]furan **4a** was observed after 48 hours at 80 °C. However, with 20 mol % of AgOTf or $AgNTf_2$ added, **4a** was obtained in 39 % and 49 % yield, respectively (d.r. ≈ 3:1). Interestingly, with 20 mol % of AgOTf alone, a similar yield was obtained

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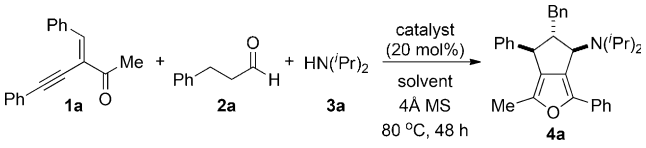
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]
1	$ClAuPPh_3$	DCE	–	–
2	$ClAuPPh_3$ + AgOTf (20 mol%)	DCE	39	77:23
3	$ClAuPPh_3$ + $AgNTf_2$ (20 mol%)	DCE	49	76:24
4	AgOTf	DCE	44	82:18
5	$ZnCl_2$	DCE	16	75:25
6	$Zn(OTf)_2$	DCE	69	81:19
7	$Sc(OTf)_3$	DCE	5	n.d.
8	$Bi(OTf)_3$	DCE	52	81:19
9	$In(OTf)_3$	DCE	61	82:18
10	$In(NTf_2)_3$	DCE	75	77:23
11	$InCl_3$	DCE	66	79:21
12	$InBr_3$	DCE	76	83:17
13	$InBr_3$ (10 mol%)	DCE	64	80:20
14[d]	**$InBr_3$**	**DCE**	**92**	**80:20**
15	$InBr_3$	CH_3CN	44	82:18
16	$InBr_3$	$CDCl_3$	53	81:19

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.20 mmol), catalyst (20 mol%), solvent (2.0 mL), and 4 Å molecular sieves (MS, 15 mg), 80 °C for 48 h. [b] Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxy benzene as an internal standard. [c] d.r. = diastereomeric ratio, determined by ^{1}H NMR analysis of the crude reaction mixture. [d] With 45 mg of 4 Å MS. DCE = 1,2-dichloroethane, n.d. = not determined.

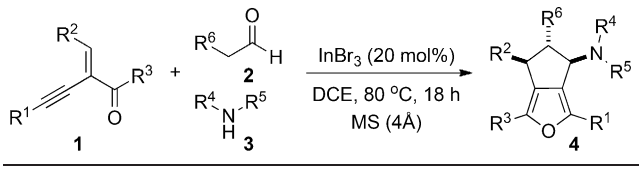
(Table 1, entry 4). The use of $ZnCl_2$ resulted in a low yield (16%) of **4a** whereas a significant increase in yield was observed with $Zn(OTf)_2$ (69%, Table 1, entries 5 and 6). For $Sc(OTf)_3$ only traces of the product were observed, while $Bi(OTf)_3$ and $In(OTf)_3$ furnished product **4a** in 52% and 61% yield, respectively (Table 1, entries 7–9). When other indium(III) salts were employed, the formation of **4a** took place in higher yields: 76% with $InBr_3$, and 75% with $In(NTf_2)_3$ (Table 1, entries 10–12).

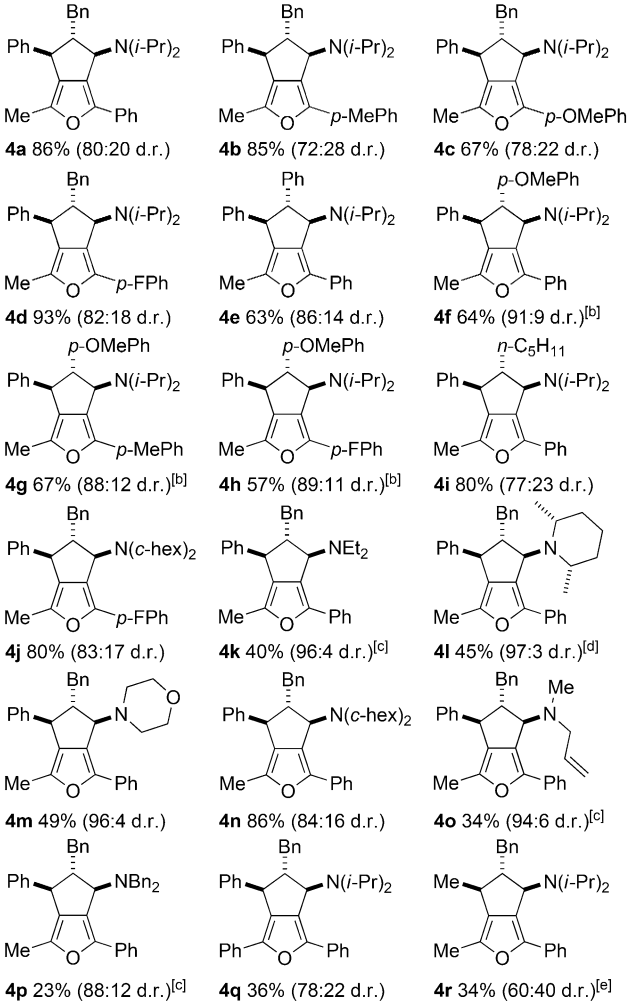
Gratifyingly, by increasing the loading of molecular sieves, **4a** was obtained in 92% yield (80:20 d.r.) after 18 hours using $InBr_3$ as the catalyst (Table 1, entry 14). Other solvents (CH_3CN and $CDCl_3$), and a lower catalyst loading (10 mol%) resulted in decreased yields (Table 1, entries 13, 15 and 16). It should be noted that the d.r. of **4a** was not significantly affected by the choice of catalyst. Furthermore, the molar ratio of the starting materials (**1**, **2** and **3**) was important to obtain high yields (see the Supporting Information for additional data).

Next, we explored the scope of this reaction (Table 2). Alkynyl enones comprising various aromatic substituents on the alkyne part (R^1) led to high yields of products **4a**–**4d**, with the exception of the methoxy-substituted derivative **4c** which was isolated in 67% yield (Table 2, **4a**–**4d**).

An improved diastereoselectivity was observed upon changing the aldehyde from **2a** to one-carbon shorter analogs. However, due to the less reactive conjugated enamines (observable by ^{1}H NMR), the yields were lower and the reactions required longer times (24 h) (Table 2, **4e**–**4h**). The

Table 2: Scope with respect to various 2-(1-alkynyl)-2-alken-1-ones, aldehydes, and amines.[a]





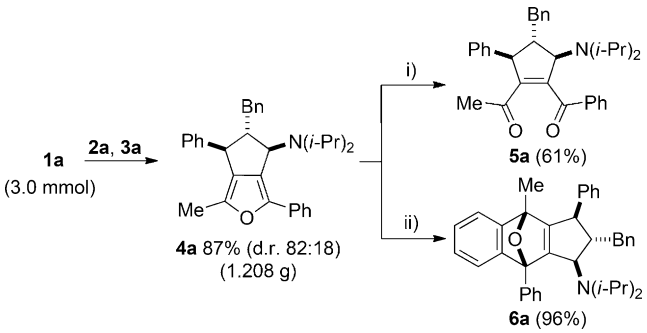
[a] Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), **3** (0.60 mmol), $InBr_3$ (20 mol%), DCE (6 mL), activated molecular sieves 4 Å (135 mg), 80 °C for 18 h. d.r. = diastereomeric ratio, determined by ^{1}H NMR analysis of the crude reaction mixture. The major diastereomers (**4**) are shown. [b] For 24 h. [c] For 6 h. [d] For 8 h. [e] For 4 h.

aliphatic aldehyde heptanal furnished cyclopenta[*c*]furan **4i** in 80% yield.

Furthermore the reaction outcome employing various secondary amines was investigated (Table 2, **4j**–**4p**). The use of dicyclohexylamine led to yields and diastereoselectivities similar to diisopropylamine (Table 2, **4j** and **4n**). However, when less sterically hindered amines were used, the d.r. improved significantly (up to 97:3 d.r., Table 2, **4k**–**m** and **4o**). Albeit the reaction times were shorter for **4k**–**l** and **4o**, the isolated yields were low (34–40%). When morpholine was used, we observed around 10% of an alkyne hydroamination product. Notably, in the absence of the catalyst, a full

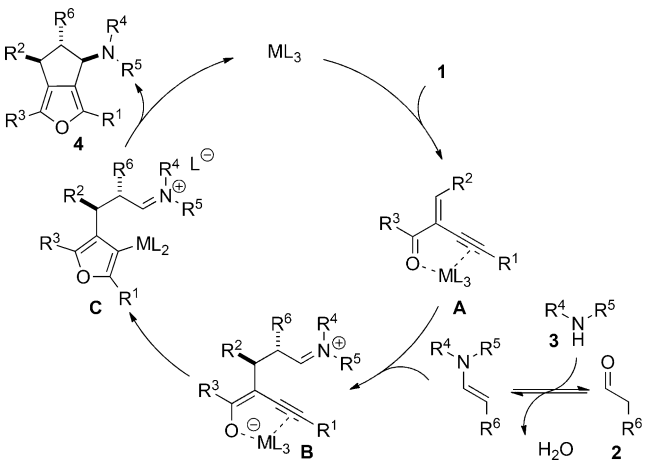
conversion into the hydroamination product was observed. With dibenzylamine, and upon alteration of the alkynyl enone substituents R^2 and R^3 we observed a lower yield, and for **4r** a poor diastereoselectivity (Table 2, **4p**–**4r**).

Gratifyingly, upon performing the three-component reaction of **1a**, **2a**, and **3a** on a larger scale, product **4a** was isolated in 87% yield (1.2 g, Scheme 2). The major diastereomer of the reaction (*major*-**4a**, separated by chromatography) was subjected to an oxidative ring-opening using *m*-CPBA to obtain **5a** in 61% yield. Furthermore, in a cycloaddition reaction of *major*-**4a** with an in situ generated benzyne, **6a** was obtained in 96% yield as a single diastereomer.[10]



Scheme 2. Synthesis of **4a** on a 3.0 mmol scale, and transformations of the major diastereomer: i) Oxidation with *m*-CPBA; ii) cycloaddition with benzyne.

For the metal-catalyzed cyclization reactions with alkynyl enones, two possible pathways were proposed by Larock.[6] An initial formation of the furan ring followed by a nucleophilic attack was envisioned for catalysts displaying an efficient alkyne π-activation. For more oxophilic Lewis acids, the reaction was proposed to be initiated by a Michael addition. As $ClAuPPh_3$ does not catalyze the transformation described herein, we propose a catalytic cycle initiated by a nucleophilic attack of the in situ generated enamine on the activated enone (Scheme 3, **A**). From the resulting intermediate **B**, one can envision formation of product **4**, via intermediate **C** (Scheme 3).



Scheme 3. Proposed mechanism.

The stereochemical outcome of the reaction is controlled by a selective bond formation between alkynyl enone **1** and the enamine. The second cyclization step proceeds with a high level of selectivity, most likely governed by the sterics of the amine substituents (c.f. Table 2). The relative stereochemistry (of both diastereomers of product **4a**) was determined by differential NOE experiments, and confirmed by an X-ray analysis of **6a**.[10]

In summary, an efficient Lewis acid-catalyzed three-component cyclization reaction of aliphatic aldehydes, secondary amines and alkynyl enones was developed. The transformation proceeds in moderate to excellent selectivity, obtaining cyclopenta[*c*]furans comprising a variety of substituents. Excellent diastereomeric ratios were observed for less bulky amines, whereas the isolated yields typically were higher when diisopropylamine was used. We propose that indium catalysts, which proved to be the most competent catalysts for this transformation, are mainly operating via activation of the enone moiety.

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Keywords: alkynes · enones · fused-ring systems · indium catalysis · multicomponent reactions

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[10] CCDC 1476592 (**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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