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Asymmetric Synthesis of Hexahydropyrrolo-isoquinolines by an Organocatalytic Three-Component Reaction

Alberto Fraile, Daniele M. Scarpino Schietroma, Anna Albrecht, Rebecca L. Davis, and Karl Anker Jørgensen*[a]

The pyrrolo-isoquinoline moiety[1] is present in alkaloid families such as erythrines,[2] lamellarins,[3] and pyrrolo[2,1-*a*]isoquinoline derivatives,[4,5] all of which exhibit biological activities. The importance of this heterocyclic system is further enhanced by its utility as an intermediate for the synthesis of alkaloids.[1] Consequently, the interest in new synthetic methodologies for this moiety has increased.[6] Three strategies have been developed for the asymmetric construction of polyhydropyrrolo[2,1-*a*]isoquinoline derivatives: a) *N*-acyliminium cyclization,[7] b) Mitsunobu reaction of optically pure 3-(tetrahydroisoquinolin-1-yl)propan-1-oles,[4a,8] and c) asymmetric hydrogenation of prochiral iminium salts with a chiral metal complex.[4b,9] A diastereoselective route to this moiety involving a [3+2]-cycloaddition of 3,4-dihydroisoquinolinium ylides to chiral dipolarophiles was recently presented.[10]

One strategy to optically active polysubstituted pyrrolidines is the metal-[11] or organocatalyzed[11c,12] [3+2]-cycloaddition of alkenes with azomethines. However, these reactions focus on α-iminoesters as azomethine ylide precursors and only recently has an organocatalytic [3+2]-cycloaddition of azomethine ylides to α,β-unsaturated aldehydes been presented.[13]

Herein we present a new multicomponent[14] concept for the construction of hexahydropyrrolo[2,1-*a*]isoquinoline derivatives. The concept is based on a [3+2]-cycloaddition reaction of in situ generated dihydroisoquinolinium ylides, from the corresponding imines and α-bromoesters or ketone,[15] to α,β-unsaturated aldehydes, and is catalyzed by a chiral pyrrolidine in the presence of a base (Scheme 1). This multicomponent approach allows the formation of two new C–C bonds, a C–N bond, and four stereocenters in one-step.

The three-component reaction between 6,7-dimethoxy-3,4-dihydroisoquinoline HCl (**1a**), methyl 2-bromopropanoate (**2a**), and cinnamic aldehyde (**3a**) was the model system for optimization of the experimental parameters.[16]

[a] Dr. A. Fraile, D. M. Scarpino Schietroma, Dr. A. Albrecht, Dr. R. L. Davis, Prof. Dr. K. A. Jørgensen
Center for Catalysis, Department of Chemistry
Aarhus University, 8000 Aarhus C (Denmark)
Fax: (+45) 8715-5956
E-mail: kaj@chem.au.dk

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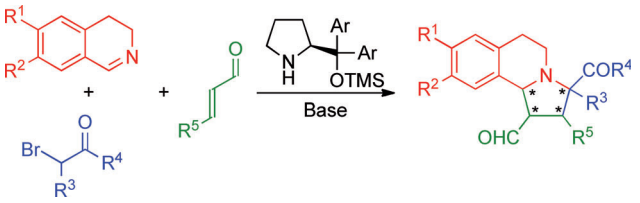
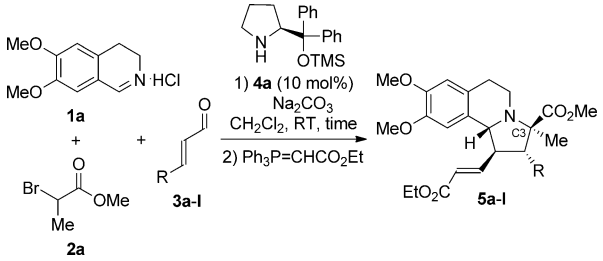


Scheme 1. Asymmetric synthesis of hexahydropyrrolo[2,1-*a*]isoquinolines by three-component organocatalytic cycloaddition.

(*S*)-2-(Diphenyl(trimethylsilyloxy)methyl)pyrrolidine (**4a**),[17] Na_2CO_3, CH_2Cl_2, and room temperature were the best conditions for the [3+2]-cycloaddition and gave the optically active product, as the conjugated ester **5a**, in high yields, good diastereoselectivity and an excellent enantioselectivity of 95% *ee*.

The scope of the three-component [3+2]-cycloaddition using different α,β-unsaturated aldehydes is given in Table 1.

Table 1. Results for the reaction between imine **1a**, α-bromoacetate **2a**, and α,β-unsaturated aldehydes **3a–l**.[a]



Entry	R	Time [h]	Yield [%][b]	d.r.[c] (**5**/**5'**)	*ee* [%][d]
1	Ph-**3a**	26	67 (52)	78:22	95
2	4-MeO-C_6H_4-**3b**	23	85 (70)	82:18	98
3	2-MeO-C_6H_4-**3c**	31	80 (69)	82:18	98
4	4-Me-C_6H_4-**3d**	21	73 (55)	77:23	97
5	2-Me-C_6H_4-**3e**	26	62 (45)	74:26	98
6	3,5-$(Me)_2$-C_6H_3-**3f**	26	71 (53)	74:26	96
7	4-*t*Bu-C_6H_4-**3g**	49	80 (63)	79:21	96
8	4-Cl-C_6H_4-**3h**	31	68 (49)	74:26	90
9	2-Furyl-**3i**	74	58 (38)	66:34	95 [97]
10	4-CF_3-C_6H_4-**3j**	42	89 (55)	63:37	90 [89]
11	2-Naphthyl-**3k**	29	85 (61)	77:23	95
12	Et-**3l**	24	n.r.	–	–

[a] Reaction conditions and separation details, see Supporting Information. [b] Combined yield of both diastereoisomers after FC. Yield of major diastereoisomer in parentheses. [c] Stereoisomer **5'** is inverted at C3. [d] *ee* of minor diastereoisomer in brackets.

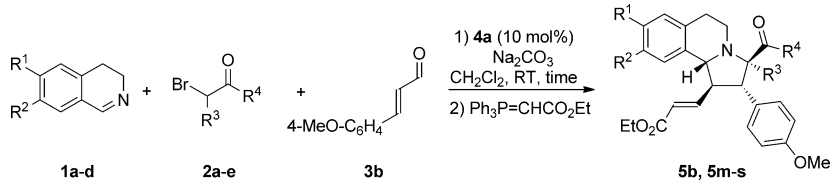
The stereoselectivity and reactivity were scarcely affected by the incorporation of electron-donating substituents on the aromatic ring, such as methoxy (Table 1, entries 1–3), methyl (entries 4–6), or *tert*-butyl (entry 7) groups, and excellent enantioselectivities were obtained. The presence of a chlorine on the aromatic ring (entry 8) led to similar results, but slightly lower enantioselectivity (90% *ee*). However, the diastereoselectivity decreased when the furyl or an aromatic ring bearing an electron-withdrawing group, such as trifluoromethyl was present (entries 9 and 10). In the case of the furyl-substituted α,β-unsaturated aldehyde (entry 9) the reactivity was low, resulting in longer reaction time and lower yield. Moreover, the naphthyl moiety (entry 11) was tolerated in the cycloaddition. It is noteworthy that all the α,β-unsaturated aldehydes used provided high enantioselectivity (more than 89% *ee*), in particular for electron-donating substituents (96–98% *ee*). The possibility to employ aliphatic enal as the dipolarophile was also evaluated (entry 12). However, the reaction gave no conversion under the standard conditions. The reaction can be scaled up to 1 mmol for aldehyde **3b** and the product was obtained with similar results in terms of yield and selectivity.[16]

The behavior of different imines **1** and α-bromo derivatives **2** was studied to evaluate the electronic influence of **1** and the size of the substituents in **2** on the reaction outcome. The reaction between imine **1a**, α-bromoester **2a**, and aldehyde **3b** was chosen as a model for this purpose (Table 2, entry 1). Employing the methyl 2-bromobutanoate **2b** (entry 2) resulted in a slight decrease in yield and stereoselectivity. The introduction of an ethoxy or phenoxy group (entries 3 and 4) resulted in comparable yield and excellent enantioselectivity, and gave increased diastereoselectivity. Interestingly, replacing the propanoate **2a** by 2-bromo-1-phenylpropan-1-one (**2e**) led to an increase in diastereoselectivity (compare Table 2, entries 1 and 5). The enhanced selectivity could be due to more steric hindrance of the carbonyl group compared to the ester moiety in the model reaction, which renders the formation of adduct **5p** more favored than **5′p**. The reaction was not affected by changes in the substituents of the imine **1**. 3,4-Dihydroisoquinoline (**1b**), 7-methyl-3,4-dihydroisoquinoline (**1c**), and 6-bromo-7-methoxy-3,4-dihydroisoquinoline (**1d**, Table 2, entries 6–8) all gave the product in good yield and enantioselectivity.

The versatility of the products obtained by the three-component [3+2]-cycloaddition is further enhanced by the transformations shown in Scheme 2. The importance of alkynes[18] encouraged us to perform the homologation of **6** in an attempt to obtain a terminal alkyne. Treatment of **6** with the Ohira–Bestmann reagent,[19] afforded the alkyne **7** in excellent yield without affecting the stereochemistry. The absolute configuration of the product was determined for the hydrochloride salt of **7** (see the Supporting Information, for structures of the major and minor diastereomers). To prove the versatility of alkyne **7**, we performed a Sonogashira coupling under mild conditions, obtaining the aryl derivative **8** in good yield. Alternatively, the reaction of **6** with the Levine reagent[20] and subsequent hydrolysis with *p*-TsOH in acetone yielded a new aldehyde **9** with an additional carbon atom after two steps.

A computational study was undertaken to provide insight into the mechanism and selectivity of the [3+2]-cycloaddition (Scheme 3).[21] A conformational analysis of the ylide intermediate shows intermediate **A** to be favored over **B** by 2.2 kcal mol^{-1}.[22] This conformational preference results from an unfavorable steric interaction between the methyl group and the hydrogens on the sp^3-carbon atom of the heterocycle.[23] Interestingly, the lower energy conformation of the ylide does not lead to the major diastereomer of the product. To obtain the major diastereomer of the reaction, the [3+2]-cyclization must proceed through the higher energy conformer of the intermediate **B**. To understand why the reaction proceeds more readily with the higher energy

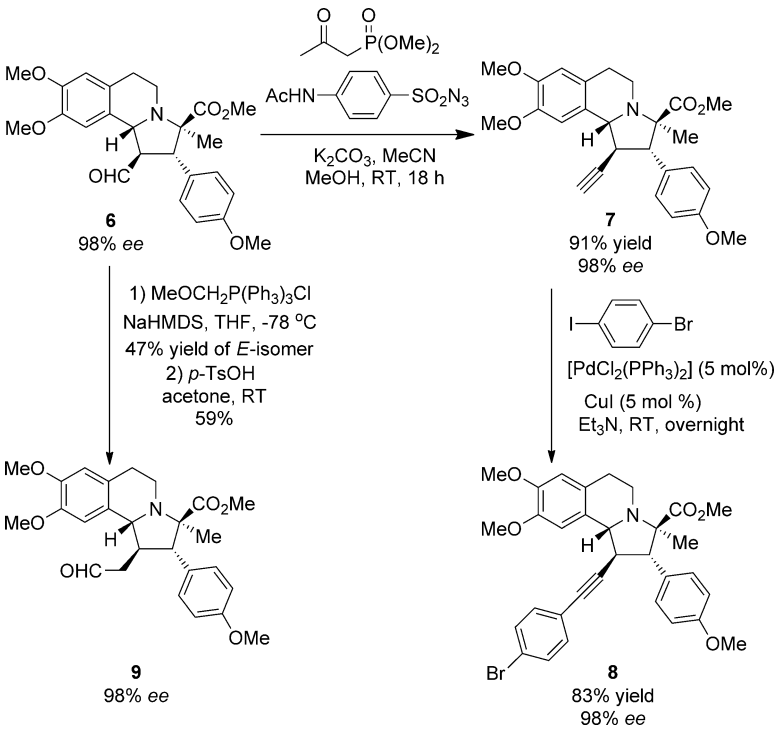
Table 2. Results indicating the scope of the organocatalytic three-component reaction of imines **1a–d**, α-bromoalkanes **2a–e**, and α,β-unsaturated aldehyde **3b**.[a]



1a-d 2a-e 3b 5b, 5m-s

Entry	Product	R^1	R^2	Imine	R^3	R^4	Bromoalkane	Time	Yield [%][b]	d.r. (**5**/**5′**)[c]	*ee* [%]
1	**5b**	OMe	OMe	**1a·HCl**	Me	OMe	**2a**	23 h	85 (70)	82:18	98
2	**5m**	OMe	OMe	**1a·HCl**	Et	OMe	**2b**	52 h	69 (52)	76:24	96
3	**5n**	OMe	OMe	**1a·HCl**	Me	OEt	**2c**	26 h	84 (69)	84:16	98
4	**5o**	OMe	OMe	**1a·HCl**	Me	OPh	**2d**	26 h	84 (68)	84:16	98
5	**5p**	OMe	OMe	**1a·HCl**	Me	Ph	**2e**	12 h	84 (77)	90:10	99
6	**5q**	H	H	**1b**	Me	OMe	**2a**	42 h	83 (61)	86:14	99
7	**5r**	H	Me	**1c**	Me	OMe	**2a**	38 h	62 (50)	81:19	99
8	**5s**	Br	OMe	**1d**	Me	OMe	**2a**	50 h	69 (65)	>95	99

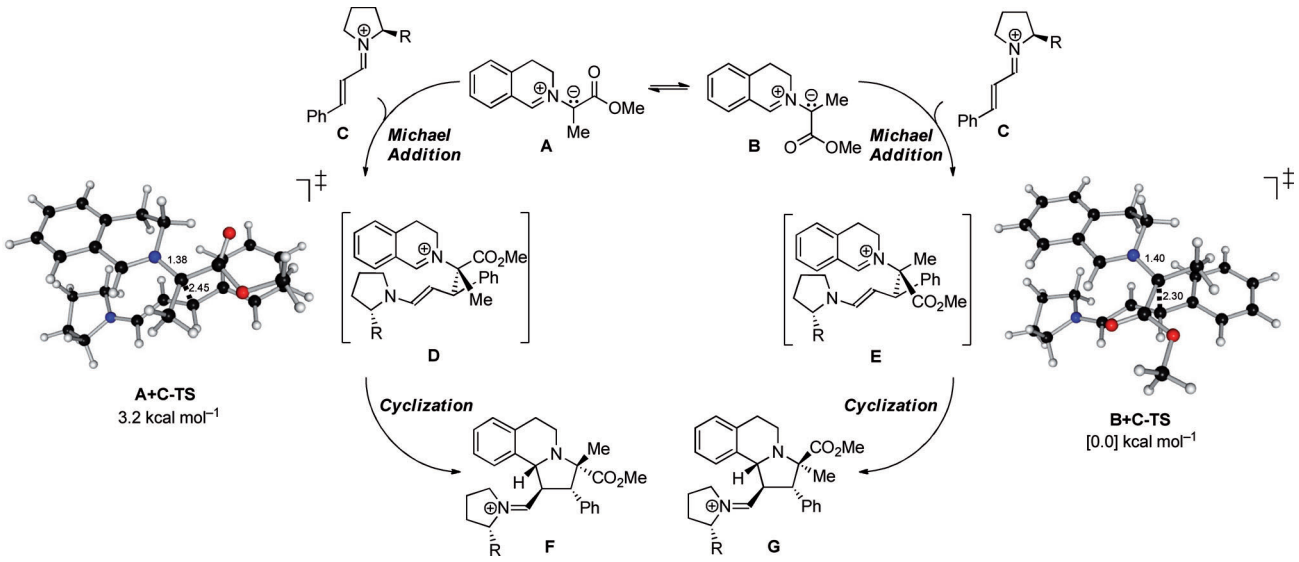
[a] For reaction conditions and separation details see Supporting Information. [b] Yield after FC. Yield of major diastereoisomer in parentheses. [c] Stereoisomer **5'** is inverted at C3.



Scheme 2. Representative transformations.

conformer of the ylide, the mechanism of the [3+2]-cycloaddition was examined computationally. Each conformer of the ylide can react with the iminium-ion **C** from two orientations; the iminium ion can be placed over the dihydroisoquinoline subunit, or the phenyl ring can be oriented over the dihydroisoquinoline subunit. This results in four possible reaction pathways from the unhindered face of **C**. However, the reaction pathways where the phenyl ring is placed above the heterocycle were calculated to have higher activation energies and higher energy products than the two pathways in which the iminium ion is placed over the heterocycle and will not be further discussed in this section.

The reactions of **A** or **B** with **C**, with the iminium ion placed over the heterocycle leading to intermediate **D** and **E** (**E** is calculated to be 1.5 kcal mol^{-1} lower in energy than **D**) are calculated to be stepwise processes (Scheme 3). The first step involves a Michael addition of the ylide to the γ-carbon atom of the iminium ion. The Michael addition is followed by cyclization of the cationic intermediate. In both pathways, the Michael addition step has a higher activation energy than the cyclization step.[16] The transition state structure for the Michael addition between **A** and **C** (**A+C-TS**) is found to be 3.2 kcal mol^{-1} higher than that for the reaction of **B** and **C** (**B+C-TS**). This energy difference is due to steric interactions between the ester and the phenyl ring in **A+C-TS** (Scheme 3). Examination of the cyclized intermediates of the [3+2]-cyclization (**F** and **G**) shows that **G**, which results from the reaction of the higher energy ylide intermediate **B**, is favored over **F** by 5.2 kcal mol^{-1}. Based on these results, the reaction path of **B** with **C** is found to be both the thermodynamically and kinetically favored reaction course.



Scheme 3. Proposed mechanism for [3+2]-cycloaddition, and transition state structures and energies for the Michael addition of **A** and **C** and **B** and **C**. Energies are reported in kcal mol^{-1} and are relative to the lower energy structure (**B+C-TS**). Bond lengths in Ångstroms.

In conclusion, the development of a three-component organocatalytic asymmetric reaction of imines, α-bromoesters or ketone with α,β-unsaturated aldehydes to give optically active pyrrolo-isoquinolines, an important class of molecules in life science, has been achieved. The reaction proceeds with excellent enantioselectivity for a large number of substituent patterns, and a series of transformations of the products obtained are demonstrated. Computational studies account for the stereoselective outcome of the reaction and show that it proceeds in a stepwise manner by a combined kinetically and thermodynamically controlled reaction path.

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Keywords: asymmetric catalysis · azomethine ylides · cycloaddition · organocatalysis · pyrroloisoquinolines

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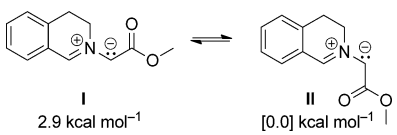
[21] Calculations were performed with GAUSSIAN09. Geometries were optimized without symmetry constraints at the M06–2X/6–31G+(d,p) (see ref. Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215) level of theory in the gas phase. See Supporting Information for the complete references on theoretical methods.

[22] All conformers of the ylide were calculated. Only the two conformers with the lowest energies are presented in the text. For structures and energies of other conformers see Supporting Information.

[23] It has been proposed that isoquinolinium ylides with conjugated esters prefer to take on a conformation in which the carbonyl oxygen atom is directed toward the iminium carbon **II** (see ref: O. Tsuge, S. Kanemasa, S. Takenaka, *Bull. Chem. Soc. Japan* **1985**, *58*, 3137). Calculations on the dihydroisoquinonlium ylide with the methyl group replaced with a hydrogen show that the energetic preference switches and **II** favored over **I** by 2.9 kcal mol^{-1} kcal mol^{-1}.



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