ORGANIC LETTERS

2013
Vol. 15, No. 12
3042–3045

Asymmetric Synthesis of Druglike Six-Membered Spirooxindoles through an Amino Enyne Catalysis

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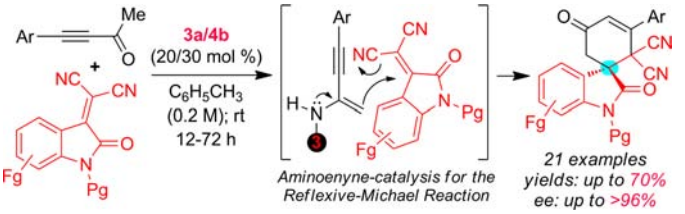
Received May 2, 2013

ABSTRACT



An effective *reflexive*-Michael (*r*-M) reaction has been disclosed to access drug-like six-membered spirooxindoles in good yields and excellent enantioselectivities by using an *aminoenyne*-catalysis.

A spirooxindole core structure is the centerpiece of a wide variety of natural and unnatural compounds that exhibit diverse biological activities.[1] Although great progress has been made toward the asymmetric synthesis of spirooxindoles, new approaches that can accomplish the simultaneous creation of spiro quaternary centers with multiple chiral centers are still in high demand.[2] In particular, the stereocontrolled high-yielding synthesis of functionalized six-membered spirooxindoles from the more environmentally friendly substrates and catalysts in a catalytic asymmetric manner are still limited.[3,4] Thus, an enantioselective catalytic approach for the direct construction of six-membered spirooxindole skeletons is a significant challenge.

Recently, we have developed an *organo-click* strategy for the construction of oxindoles with a quaternary C-3 center.[5] Later, it was recognized that the functionalized six-membered spirooxindole core structure is featured in a number of natural products as well as medicinally relevant compounds (Figure 1),[1] but its stereocontrolled asymmetric

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10.1021/ol401227q
Published on Web 05/31/2013

synthesis with spiro-quaternary stereocenter poses a great synthetic challenge. Only a few asymmetric transformations have proven suitable for achieving this challenging goal.[3,4]

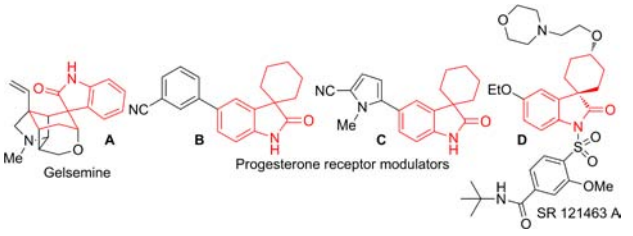

Figure 1. Medicinally important spirooxindoles.

To address this synthetic challenge, we sought to design an organocatalytic *reflexive*-Michael (*r*-M) reaction that would involve a reaction between two simple and readily available starting materials. Given the recent discovery of *2-aminobuta-1,3-enynes* (*amino enynes*) as mild nucleophiles in the organocatalytic *r*-M and aldol reactions,[6] we envisioned that *r*-M reactions between unmodified ynones **1** and 2-(2-oxoindolin-3-ylidene)malononitriles **2** would yield the desired spirooxindole skeletons in a highly stereoselective manner (Scheme 1). From the pioneering studies of Deng and other co-workers on cinchona alkaloid catalysis[7] and also from our own findings on these class of catalysts,[8] we focused our attention to use this class of organocatalysts (Scheme 1). Herein, we present novel organocatalytic asymmetric *r*-M reactions between unmodified ynones **1** and 2-(2-oxoindolin-3-ylidene)malononitriles **2** that would provide the highly functionalized six-membered spirooxindoles **5** in good yields with high enantioselectivities.

Scheme 1. Design for Spirooxindole Synthesis through an Amino Enyne Catalysis

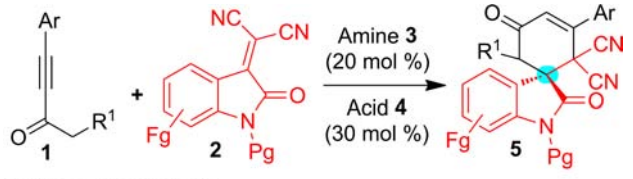

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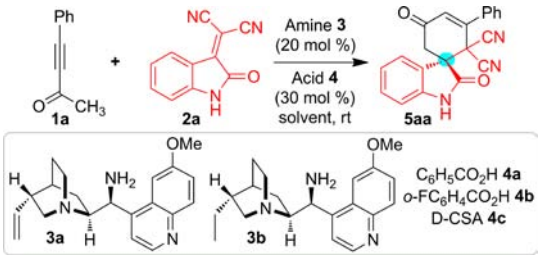
Table 1. Reaction Preliminary Optimization[a]



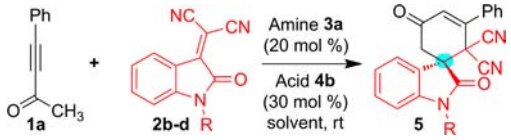
entry	catalyst **3/4** (20/30 mol %)	solvent (0.2 M)	time (h)	yield[b] (%) of **5aa**	ee[c] (%) of **5aa**
1	**3a**	$C_5H_5CH_3$	72	27	27
2	**3a/4a**	$C_6H_5CH_3$	72	50	85
3	**3a/4b**	$\mathbf{C_6H_5CH_3}$	**72**	**70**	**92**
4[d]	**3a/4b**	$C_6H_5CH_3$	36	70	85
5[d]	**3b/4b**	$C_5H_5CH_3$	12	60	87
6	**3a/4b**	DCM	72	60	88
7	**3a/4b**	**DCE**	**60**	**68**	**93**
8[e]	**3a/4b**	DCE	60	70	90
9	**3b/4b**	DCE	72	60	86
10[d]	**3a/4b**	DCE	36	55	84
11	**3a/4c**	$C_6H_5CH_3$	72		
12	**3a/4b**	CH_3CN	72		

[a] Reactions were carried out in solvent (0.2 M) with 2 equiv of **1a** relative to the **2a** (0.2 mmol) in the presence of 20/30 mol % of catalyst **3/4**. [b] Yield refers to the column-purified product. [c] Ee determined by CSP HPLC analysis. [d] Reaction performed at 60 °C. [e] Co-catalyst **4b** was taken as 40 mol %.

We initiated our studies by evaluating the *r*-M reaction between ynone **1a** and 2-(2-oxoindolin-3-ylidene)-malononitrile **2a** using *epi*-quinine-NH_2 **3a** as the catalyst in toluene at 25 °C (Table 1, entry 1). We found that the reaction proceeded in very poor manner and afforded the desired product **5aa** in low yield with poor selectivity. Surprisingly, the same reaction with benzoic acid **4a** as the cocatalyst at 25 °C for 72 h furnished the chiral spirooxindole (−)-**5aa** in 50% yield with 85% ee (Table 1, entry 2). After thorough investigation of *epi*-quinine-NH_2 **3a**-catalyzed asymmetric *r*-M reaction, we found that the solvent, cocatalyst, and temperature have significant effect on the ee's and yields. Subsequent optimization studies, we obtained the high enantioselectivities (up to 93% ee) with the combination of *epi*-quinine-NH_2 **3a** and *o*-$FC_6H_4CO_2H$ **4b** as cocatalyst in DCE or toluene (Table 1). In the final optimization, asymmetric *r*-M reaction of **1a** and **2a** through **3a/4b**-catalysis in toluene at 25 °C for 72 h furnished the chiral spirooxindole (−)-**5aa** in 70% yield with 92% ee (Table 1, entry 3). The same *r*-M reaction in DCE furnished the (−)-**5aa** in 68% yield with 93% ee (Table 1, entry 7).

We were interested in testing the electronic factor of *N*-substitution and also the solvent factor between toluene/DCE of the designed *r*-M reaction (Table 2). Reaction of **1a** with 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile **2b** under the catalysis of **3a**/**4b** in toluene at 25 °C for 72 h

Table 2. *N*-Substitution Effect on the *r*-M Reaction



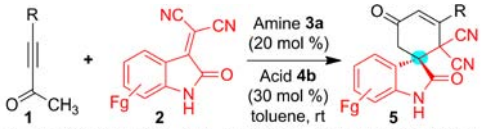
entry	R	solvent (0.2 M)	time (h)	yield[a] (%) of 5ab–ad	ee[b] (%) 5ab–ad
1	**2b:** Me	$C_6H_5CH_3$	72	**5ab** (50)	93
2	**2b:** Me	DCE	48	**5ab** (58)	86
3	**2c:** CH_2OMe	$C_6H_5CH_3$	36	**5ac** (50)	88
4	**2c:** CH_2OMe	DCE	12	**5ac** (50)	82
5	**2d:** $COCH_3$	DCE	72	**5ad** (<10)	

[a] Yield refers to the column-purified product. [b] Ee determined by CSP HPLC analysis.

furnished the (−)-**5ab** in 50% yield with 93% ee (Table 2, entry 1). Interestingly, the same reaction in DCE at 25 °C for 48 h furnished the (−)-**5ab** in 58% yield with reduced (86%) ee (Table 2, entry 2). In a similar manner, *r*-M reaction of **1a** with 2-(1-(methoxymethyl)-2-oxoindolin-3-ylidene)malononitrile **2c** under **3a**/**4b**-catalysis in toluene at 25 °C for 36 h furnished the (−)-**5ac** in 50% yield with 88% ee and the same reaction in DCE gave the (−)-**5ac** in 50% yield with reduced (82%) ee (Table 2, entries 3−4). Surprisingly, rate of the *r*-M reaction between **1a** and 2-(1-acetyl-2-oxoindolin-3-ylidene)malononitrile **2d** under the **3a**/**4b**-catalysis is very slow (Table 2, entry 5). In a further understanding of the reaction, we treated **1a** with **2c** in DCE at 25 °C for 72 h under the 9-*epi*-aminoquinine thiourea **3c**-catalysis to furnish the only Michael adduct **6ac** in < 10% yield (eq S1, Supporting Information). This result clearly explaining that the nucleophilic nature of **3**, acidic/counteranion nature of **4** and also nature of olefin **2** is crucial for the success of designed *r*-M reaction.

After realizing the electronic factors of *N*-substitution and also toluene as the best solvent, we further explored scope of the *epi*-quinine-NH_2/*o*-$FC_6H_4CO_2H$-catalyzed *r*-M reaction by developing diversity-oriented synthesis of optically pure spirooxindoles **5** through the reaction of ynones **1a**−**h** with olefins **2a**−**j** (Table 3). The chiral spirooxindoles **5** were obtained in good yields and excellent ee's with variety of olefins containing neutral, electron-donating, electron-withdrawing, and halogenated **2a**−**j** and ynones containing neutral, electron-donating, halogenated and heteroatom substituted **1a**−**h** from the asymmetric *r*-M reaction (Table 3). Herein, variety of unmodified ynones **1a**−**h** are used as source for the in situ generation of 2-aminobuta-1,3-enynes as novel mild nucleophiles in a *r*-M reaction to furnish the functionalized drug-like spirooxindoles **5ba**−**bj** with up to > 96% ee in good yields (Table 3). Surprisingly, the *r*-M reaction of aliphatic ynone 4-(trimethylsilyl)but-3-yn-2-one **1h** with **2c** under the catalysis of **3a**/**4b** furnished the directly desilylation product (+)-**5hc** (R = H) in 40% yield with 81% ee

Table 3. Scope of the Asymmetric Amino Enyne Catalysis



R = Ph (**1a**), 4-MeC_6H_4 (**1b**), 4-$MeOC_6H_4$ (**1c**), 4-$MeOCH_2OC_6H_4$ (**1d**), 4-FC_6H_4 (**1e**), 4-ClC_6H_4 (**1f**), 2-Thiophenyl (**1g**), and Me_3Si (**1h**)

Fg = 5-F (**2e**), 5-Cl (**2f**), 5-Br (**2g**), 5-I (**2h**), 5-NO_2 (**2i**), and 5,7-Me_2 (**2j**)

entry	ynone 1	olefin 2	time (h)	products	yield[a] (%)	ee for 5[b] (%)
1	**1b**	**2a**	60	**5ba**	60	90
2	**1c**	**2a**	60	**5ca**	60	93
3	**1d**	**2a**	48	**5da**	50	91
4	**1e**	**2a**	60	**5ea**	60	89
5	**1f**	**2a**	60	**5fa**	55	85
6	**1g**	**2c**	60	**5gc**	50	88
7[c]	**1h**	**2c**	72	**5hc**	40	81
8	**1b**	**2e**	72	**5be**	50	92
9	**1c**	**2e**	60	**5ce**	50	96
10	**1a**	**2f**	72	**5af**	55	88
11	**1a**	**2g**	72	**5ag**	50	87
12	**1a**	**2h**	72	**5ah**	50	90
13	**1b**	**2i**	120	**5bi**	40	85
14	**1b**	**2j**	72	**5bj**	40	91

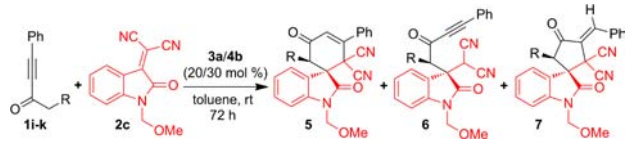
[a] Yield refers to the column-purified product. [b] Ee determined by CSP HPLC analysis. [c] Product **5hc** obtained as desilylation product (R = H).

(Table 3, entry 7). Interestingly, the *r*-M reaction of ynone containing α′-branched aliphatic group **1i** with **2c** under the **3a**/**4b** catalysis furnished the unexpected cyclopentanulation product **7ic** in 40% yield with > 99% de and < 5% ee (Table 4, entry 1). In a similar manner, reaction of ynone **1j** with **2c** also furnished the cyclopentanulation product **7jc** in 40% yield with > 99% de and < 5% ee (Table 4, entry 2). But the reaction of benzyloxy ynone **1k** with **2c** under the **3a**/**4b** catalysis gave the Michael product **6kc** in 40% yield with > 99% de and 95% ee (Table 4, entry 3). These results clearly indicating that the ynones **1i**−**k** containing α′-branched substitution is controlling enough to generate the reactive intermediate species like 2-aminobuta-1,3-enynes versus 4-aminobuta-3-en-2-ones with catalyst *epi*-quinine-NH_2 through 1,2- or 1,4-addition and which are the responsible for six-membered versus five-membered ring formation, respectively. The structure and absolute stereochemistry of the products **5**-**7** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (−)-**5af** and **7ic** as shown in Figures S1 and S2 (Supporting Information).[9]

With the synthetic applications in mind, we explored the utilization of spiranes **5** in the high-yielding synthesis of functionalized chiral spiranes **8** and **9** via simple reduction and chlorination reactions (Scheme 2). High-yielding reduction of chiral spirooxindoles (−)-**5ag** and (−)-**5ac** with

(9) CCDC-927184 for (−)-**5af** and CCDC-927185 for **7ic** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

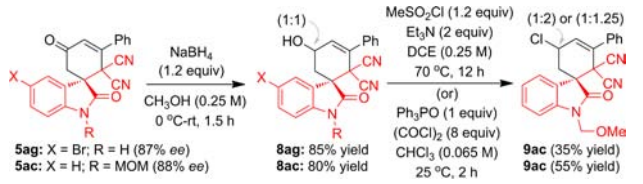
Table 4. Designed *r*-M Reaction with Other Ynones



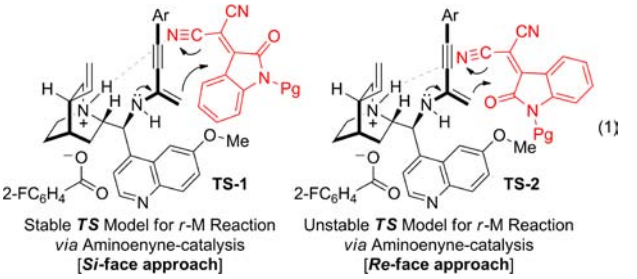
		yield (%)				
entry	R	product **5**	product **6**	product **7**	de **6/7** (%)	ee **6/7** (%)
1	CH_3 (**1i**)			**7ic** (40)	>99	<5
2	CH_2CH_3 (**1j**)			**7jc** (40)	>99	<5
3	OBn (**1k**)		**6kc** (40)		>99	95

1.2 equiv of $NaBH_4$ in dry CH_3OH at 0−25 °C for 1.5 h furnished the allylic alcohols (−)-**8ag** and (−)-**8ac** in 80−85% yield with 87−88% ee and 1:1 dr, respectively (Scheme 2). Interestingly, diastereomerically pure allylic alcohols (−)-**8ag** and (−)-**8ac** were separated through column chromatography. Surprisingly, treatment of the chiral allylic alcohol (−)-**8ac** with 1.2 equiv of $MeSO_2Cl$ and Et_3N in dry DCE at 70 °C for 12 h furnished the chlorination product (+)-**9ac** in 35% yield with 88% ee and 1:2 dr instead of simple mesylation or elimination products. In a similar manner, treatment of (−)-**8ac** with 1.0 equiv of Ph_3PO and 8.0 equiv of $(COCl)_2$ in dry $CHCl_3$ at 25 °C for 2 h furnished the chlorination product (+)-**9ac** in 55% yield with 88% ee and 1:1.25 dr. Diastereomerically pure allyl chlorides (+)-**9ac** were separated through column chromatography. Compounds (−)-**8ac**, (−)-**8ag**, and (+)-**9ac** would be precursors for the synthesis of druglike molecules as shown in the Figure 1.

Scheme 2. Synthetic Applications of Chiral Spirooxindoles



Although supplementary studies are needed to securely elucidate the mechanism of *r*-M reactions through **3a/4b**-catalysis, the reaction proceeds by stepwise manner between in situ generated 2-aminobuta-1,3-enynes or 4-aminobuta-3-en-2-ones with olefins **2** (eq 1). Based on the crystal structure studies, we can rationalize the observed high stereoselectivity through an allowed transition state where the *si*-face of olefin **2** approaches the *si*-face of 2-aminobuta-1,3-enynes (amino enynes) due to the strong hydrogen-bonding/electrostatic attraction/CH-π and halogen (F)−π interactions[10] and less steric hindrance/electrostatic repulsion as shown in the **TS-1**. Formation of the minor enantiomer may be explained by model **TS-2**, in which there is strong electrostatic repulsions between the amine/methoxy portion of the catalyst and the carbonyl/amine group of olefins **2** (eq 1). Formation of the unexpected cyclopentanulation products **7** may be explained through stepwise reaction between in situ generated 4-aminobuta-3-en-2-ones with olefins **2** as similar to the Tomita phosphine-catalyzed zipper cyclization (see full details in the Scheme S1, Supporting Information).[11b]



In summary, building on a powerful but largely unexploited mode of catalytic amino enyne reactivity discovered by Gouverneur and our group,[6] we have developed a versatile new method for the room-temperature synthesis of functionalized chiral spirooxindoles **5** from acyclic precursors. The products of the *r*-M reaction **5** were derivatized with good to moderate diastereoselection into an array of highly functionalized druglike molecules **8** and **9**. Future investigations within the group will continue to explore the scope of novel modes of catalytic amino enynes reactivity furnished by chiral amines with unmodified ynones.

Acknowledgment. This work was made possible by a grant from the DST, New Delhi. C.V. and R.M. thank CSIR, New Delhi, for their research fellowships. This work is dedicated to Professor Goverdhan Mehta (University of Hyderabad, India) on the occasion of his 70th birthday.

Supporting Information Available. Experimental procedures, compound characterization, X-ray crystal structures, and analytical data (^{1}H NMR, ^{13}C NMR, HRMS, and HPLC) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.