LETTERS

N-Heterocyclic Carbene-Catalyzed Chemoselective Cross-Aza-Benzoin Reaction of Enals with Isatin-Derived Ketimines: Access to Chiral Quaternary Aminooxindoles

Jianfeng Xu,^{†,§} Chengli Mou,^{†,‡,§} Tingshun Zhu,[†] Bao-An Song,^{*,‡} and Yonggui Robin Chi^{*,†,‡}

[†]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

[‡]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

Supporting Information

ABSTRACT: A chemo- and enantioselective cross-azabenzoin reaction between enals and isatin-derived ketimines is disclosed. The high chemoselectivity (of the acyl anion reaction over enal α - and β -carbon reactions) is enabled by the electronic and steric properties of the *N*-heterocyclic carbene organocatalyst.

he formation of different products from identical substrates in a precise and selective manner is attractive in organic synthesis. In the arena of N-heterocyclic carbene (NHČ) organocatalysis,¹ the addition of a carbene catalyst to an α_{β} -unsaturated aldehyde (enal) can lead to reactive intermediates bearing at least three reactive carbon centers of the enal: the enal β -carbon (homoenolate intermediate),² α carbon (enolate intermediate),³ and carbonly carbon (acyl anion intermediate equivalent) (Scheme 1a).⁴ In 2004, the Bode^{2a} group and Glorius^{2b} group reported the NHC-catalyzed generation of homoenolates from enals and their annulation with aldehydes to synthesize γ -lactones, in which the enal β carbon behaved as a reactive nucleophilic carbon. This homoenolate chemistry was then further extensively explored by a number of researchers, including Nair,^{2c} You,^{2d} Zhong,^{2e} Scheidt,^{2f} Rovis,^{2g} Chi,^{2h} Liu,²ⁱ and Ye.^{2j} The reactivity of the enal α -carbon has also been relatively well studied. A selective β -carbon protonation of the NHC-bound homoenolate intermediate generates an enolate intermediate with a reactive enal α -carbon that can undergo inter- and intramolecular reactions, as disclosed by Bode,^{3a} Glorius,^{3b} Scheidt,^{3c} You,^{3d} Nair,^{3e} and Chi.³

However, in contrast to enal α - and β -carbons, the enal carbonyl carbon as a reactive nucleophilic carbon (acyl anion intermediate) for asymmetric reactions is much less studied. To the best of our knowledge, so far there are only three successful examples using the carbonyl carbons of enals as nucleophiles to construct chiral building blocks. In 2011, the Rovis group reported an elegant Stetter reaction of enals with nitroalkenes using catechol as a crucial additive.^{4a} At about the same time, our group discovered a highly enantioselective Stetter reaction of enals with modified chalcones.^{4b} Very recently, Ye and coworkers developed an asymmetric benzoin reaction of enals with trifluoromethyl ketone-derived ketimines catalyzed by a chiral NHC catalyst containing a hydroxyl group.^{4c}





a) three reactive intermediates generated from addition of NHC to enal



Here we report a cross-aza-benzoin reaction of enal with isatin-derived ketimine involving the enal carbonyl carbon as a

Received: May 5, 2014 **Published:** May 30, 2014 nucleophilic reactive carbon (Scheme 1b). The reaction is highly chemoselective: potential side reactions between the enal α - and β -carbons with the ketimine substrate are either not observed or largely suppressed. The cross-aza-benzoin reaction is enantioselective and affords 3-aminooxindoles bearing a quaternary stereogenic center with high enantioselectivities. Such 3-aminooxindoles are found as core skeletons in a variety of biologically active compounds exhibiting numerous significant pharmaceutical properties, such as the vasopressin VIb receptor antagonist SSR-149415^{Sa,b} and the potent gastrin/ CCK-B receptor antagonist AG-041R.^{Sc}

Notably, the same set of substrates (enals and isatin-derived ketimines) can undergo a cyclization reaction to form γ -lactams involving the enal β -carbon as a reactive nucleophilic center (homoenolate intermediate), as previously reported by our group (Scheme 1b).^{2h} The key factor that controls the chemoselective reactions of the enal β - and carbonyl carbons is the NHC catalysts. As documented in Bode's study⁶ and indicated by reactions from others,^{7a-c} an NHC catalyst with an electron-rich, sterically bulky substituent such as the Nmesityl group on the triazolium ring favors homoenolate reactions, while the electron-deficient, less hindered azolium salts, such as the N- pentafluorophenyl derivatives, are preferred for acyl anion reactions. Specifically in our reactions (Scheme 1b), aminoindanol-derived NHC with a N-mesityl substituent previously explored by Bode favors the β -carbon pathway to form annulation products; the more electron-deficient and less bulky NHC catalyst with a N-pentafluorophenyl substituent prefers the carbonyl carbon reaction to afford cross-aza-benzoin products (Scheme 1b).

Key results for reaction optimization are summarized in Table 1. Enal 1a and isatin-derived ketimine 2a were used as the model substrates. In the absence of an NHC precatalyst, no formation of product 3a or 4a was observed (Table 1, entry 1). When aminoindanol derived precatalyst A⁸ with a N-mesityl substituent was used, the reaction afforded the homoenolatederived adduct 4a in 80% yield (entry 2), as reported in our previous^{2h} studies. Replacing the mesityl group on the NHC precatalyst A with an electron-deficient substituent, such as pentafluorophenyl (precatalyst B^9) and 2,4,6-trichlorophenyl (precatalyst C), changed the reaction outcomes and afforded the desired cross-aza-benzoin product 3a as the major product with moderate enantioselectivity (entries 3 and 4). Next we moved to identify NHC catalysts with both good chemo- and enantioselectivities and examined L-phenylalanine derived precatalysts D-F. Similar effects of the N-aryl substituent on the reaction chemoselectivities are observed. N-Mesityl substituted precatalyst D^{10} favored the homoenolate reaction (entry 5), and the NHC catalysts E^{11} and F with smaller and electron-deficient substituents favor the aza-benzoin reactions (entries 6 and 7). To our delight, NHC precatalyst F with a 2,4,6-trichlorophenyl substituent allows a clean reaction with the formation of 3a in 75% yield with excellent 97:3 er (entry 7). With F as the optimal precatalyst, we also examined the solvent effect (entries 8-12). Nonpolar solvent toluene gave product 3a in 62% yield with a slightly better 98:2 er (entry 8), while CH2Cl2 caused a slight decrease in both yield and enantioselectivity (entry 9). Polar aprotic solvents such as THF, EtOAc, and CH₃CN were not effective for this reaction (entries 10-12). Finally, we found that 10 mol % of NHC precatalyst F was enough to afford **3a** with 72% yield and 97:3 er (entry 13). The use of a substoichiometric amount of KOAc gives the desired product in a slightly lower yield with same er values



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ontry	cat	colvent	conv of 2a	yield of $3a$	yield of $4a$	er of
1 I	cat.	CUCI	(70)	(70)	(70)	Ja
1	-		0	_	_	-
2	A D		100	$(70)^{c}$	80	-
3	Б		100	81(78)	12	02:38
4	C D		100	07 (00)	13	87:15
5	Б		22	9	72	-
7	Б		100	$\frac{15}{75}$	10	-
/ 8	г Б	toluene	100	$(3)(3)^{c}$	13	27:3 08.7
9	F	CH.Cl.	100	$65(60)^{c}$	13	90.2 94·6
10	F	THE	27	10	3	-
11	F	EtOAc	52	23	6	_
12	F	CH ₂ CN	26	8	3	_
13 ^d	F	CHCh	100	$73(72)^{c}$	9	97:3
$14^{d,e}$	F	CHCl ₂	100	68	10	97:3
15 ^{<i>d,f</i>}	F	CHCl ₃	100	64	10	97:3

^{*a*}Yield estimated via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^{*b*}Enantiomeric ratio of **3a**, determined via chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned based on X-ray structure of **3e** (see Figure 1 and Supporting Information). ^{*c*}Isolated yield based on **2a**. ^{*d*}10 mol % of **F** was used. ^{*e*}0.05 mmol of KOAc was used. ^{*f*}0.02 mmol of KOAc was used.

(entries 14, 15). Since KOAc easily absorbs water in the air, we chose to use 1 equiv of KOAc, as it is easier to weigh an accurate amount of the base.

With the optimized reaction conditions in hand (Table 1, entry 13), we then evaluated the scope of this cross-aza-benzoin reaction (Scheme 2). A variety of enals with diverse electronic and steric properties were first explored. The use of cinnamaldehyde furnished the desired product 3a in 72% yield with 97:3 er. Enals with electron-donating substituents such as 4-Me and 4-OMe on their β -benzene ring led to the corresponding cross-aza-benzoin products 3b and 3c respectively in good yields and excellent enantioselectivities. The presence of electron-withdrawing groups (3-F, 4-Cl, and 4-Br) was also found to be compatible under the optimal conditions, affording products 3d-f in moderate to good yields and excellent er's. The introduction of a heteroaryl substituent such as the furyl and thienyl group provided the desired products 3g and 3h in 52% yield, 92:8 er and 53% yield, 97:3 er, respectively. It is worth noting that β -alkyl enals were tolerated. For example, crotonaldehyde and 2-hexenal reacted effectively to give products 3i (48% yield, 92:8 er) and 3j (50% yield, 93:7 er) respectively. Modifications on the isatin-derived ketimine substrates were feasible. The N-methyl substituent of imine substrate 2a could be replaced with other alkyl units such as an

Scheme 2. Scope of Reactions^a



^{*a*}Reaction for 8 h unless otherwise specified. ^{*b*} 12 h. ^{*c*} Yield of homoenolate product was around 70% estimated via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

allyl (product 3k) and benzyl substituent (product 3l). *N*-Phenyl substituted isatin-derived imine (product 3m), rarely explored in previous reactions involving an isatin-type substrate,¹² reacted effectively as well in our reaction. The substitution patterns on the isatin phenyl ring were also investigated, and the use of 5-Me, 5-OMe, and 7-Me substituted isatin derived ketimines furnished the desired products 3n-p in good yields and excellent er's. However, when isatin derived ketimines with electron-withdrawing substituents such as 5-Cl and 7-F on the isatin phenyl ring were used, the reaction favored the homoenolate pathway, affording cross-aza-benzoin products 3q and 3r in less than 10% yield.

The absolute configuration (R) of the stereogenic center in compound **3e** was unambiguously determined by X-ray crystallographic analysis (Figure 1).¹³ The configurations of other chiral quaternary 3-aminooxindole products were assigned on the assumption of a uniform mechanistic pathway.

In summary, we have developed an NHC-promoted intermolecular cross-aza-benzoin reaction of enals with isatinderived ketimines to afford chiral quaternary 3-aminooxindoles. The chemoselectivity is controlled by the NHC catalysts, with electron-deficient and sterically noncongested carbene catalysts favoring the enal acyl anion reaction pathway and aza-benzoin



Figure 1. ORTEP diagram of 3e.

reaction. The present study provides valuable motivations in searching for catalyst-controlled chemoselective reactions, allowing for convenient access to products of different scaffolds by starting from the same set of readily available substrates.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: robinchi@ntu.edu.sg. *E-mail: basong@gzu.edu.cn.

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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