Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Chemoselective and repetitive intermolecular cross-acyloin condensation reactions between a variety of aromatic and aliphatic aldehydes using a robust N-heterocyclic carbene catalyst†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

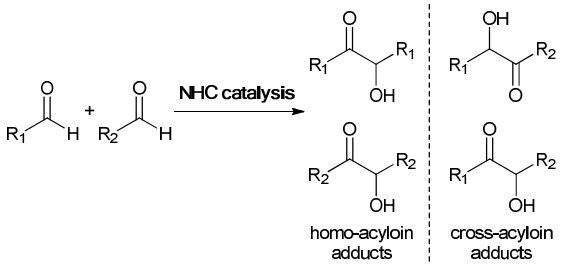
DOI: 10.1039/x0xx00000x

www.rsc.org/

Ming Yu Jin,[a‡] Sun Min Kim,[b‡] Mao Hui,[b] Do Hyun Ryu,[a] Choong Eui Song,[a] and Jung Woon Yang[b*]

We found that chemoselectivity of the crossed acyloin product is controlled by the adjustment of aromatic aldehyde/aliphatic aldehyde ratio. Moreover, we observed the persistent catalytic activity of homogeneous NHC catalyst in a solution due to NHC catalyst robustness.

Growing demand for green chemistry has made it necessary to develop a high-performance catalytic system that allows for: i) recycling of the catalyst, and ii) control of the product.[1] To meet the goals of a green approach, we choose the intermolecular crossed acyloin condensation reaction of two different aldehydes using N-heterocyclic carbene (NHC) as organocatalyst.[2-6] This reaction has an intrinsic issue with uncontrolled chemoselectivity of the products (Scheme 1)



Scheme 1 Possible products in the intermolecular crossed acyloin condensation reaction of two different aldehydes.

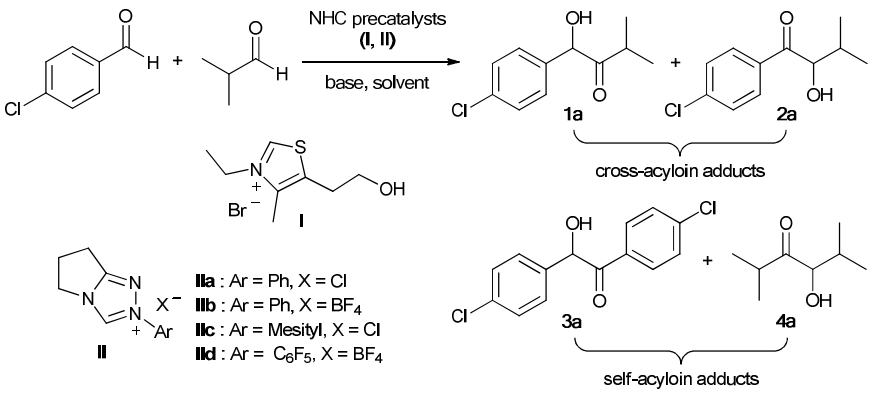
Historically, the first catalytic intermolecular cross-acyloin condensation of aromatic aldehydes and aliphatic aldehydes involving a thiazolium catalyst was reported in 1977 by Stetter and Dambkes.[2a] Recently, Zeitler and Connon pointed out that Stetter's results were not reproducible in terms of chemoselectivity and thus, re-examined chemoselectivity of the products.[2c,d] However, despite this work, the scope of the class of aromatic aldehydes in this reaction needs to be extended in order to gain widespread use. For example, higher yield and chemoselectivity were only obtained with aromatic aldehydes bearing an incorporated directing group such as a bromo group at the *ortho*-position on the aromatic ring. Namely, an *o*-bromine atom has proven to be an essential part to helping ensure high chemoselectivity. Elimination of temporary directing group was a necessary at the end of reaction in order to show the diversity of the substrate scopes. On the other hand, chloro-substituted aromatic aldehydes in either the *meta*- or *para*-position gave low chemoselectivities and chemical yields. It means that chemoselectivity was sensitive to the site of substituents on the aromatic ring. Therefore, a general solution for a chemoselective NHC-catalysed cross-acyloin reaction of two different aldehydes is still highly desirable without introduction of temporary directing group.

Herein, we describe a detailed investigation focusing on the control of chemoselectivity and chemical yield. We realized that chemoselectivity of the products were simply controlled by the adjustment of aromatic/aliphatic aldehyde ratios regardless of the electronic nature and the site of substituents on the aromatic ring. Moreover, we also demonstrate the persistent catalytic activity of homogeneous NHC catalysts in solution without any modification of catalyst backbone due to catalyst robustness.[7] To the best of our knowledge, these phenomena have not previously been described in homogeneous NHC catalysis.

Our initial investigation focused on the identification of a suitable NHC catalyst and reaction conditions for the chemoselective cross-acyloin condensation reaction of *p*-chlorobenzaldehyde with isobutyraldehyde (Table 1). A series of NHC precatalysts (**I, II**) were first used in this reaction. The results are summarized in Table 1. The use of thiazolium salt **I** and triazolium salt **IIa-c** produced the 4,4'-chlorobenzoin **3a** as a major product, which is the homo-benzoin condensation product of *p*-chlorobenzaldehyde (Table 1, entries 1-4).

Surprisingly, we observed that switching selectivity between homo- and cross-acyloin products strongly depended on the tuning of *N*-substituents on the bicyclic triazole ring backbone.

Table 1 NHC catalyst and reaction optimisation [a]



entry	NHC precatalyst	base	Isobutyraldehyde (equiv)	solvent	ratios of **1a**:**2a**:**3a** [b]	yield of **1a** (%)[c]
1	**I**	Cs_2CO_3	1.2	THF	28:10:62	22
2	**IIa**	Cs_2CO_3	1.2	THF	6:1:93	trace
3	**IIb**	Cs_2CO_3	1.2	THF	20:4:76	16
4	**IIc**	Cs_2CO_3	1.2	THF	10:17:73	9
5	**IId**	Cs_2CO_3	1.2	THF	67:2:31	50
6	**IId**	Cs_2CO_3	1.2	*m*-Xylene	75:2:23	66
7	**IId**	Cs_2CO_3	3	*m*-Xylene	82:2:16	71
8	**IId**	Cs_2CO_3	5	*m*-Xylene	89:2:9	78
9	**IId**	Cs_2CO_3	10	*m*-Xylene	93:3:4	84
10	**IId**	Cs_2CO_3	15	*m*-Xylene	94:2:4	92
11	**IId**	DBU	15	*m*-Xylene	93:3:4	89
12	**IId**	DIPEA	15	*m*-Xylene	93:2:5	74
13	**IId**	Et_3N	15	*m*-Xylene	92:3:5	74

[a] Unless otherwise specified, the reactions were performed on a 0.5-mmol scale of *p*-chlorobenzaldehyde with 1.2-15 equivalents of isobutyraldehyde, 10 mol% NHC precatalysts (**I** or **II**) and 10 mol% base at room temperature in 5.0 mL solvent. [b] Determined by ^{1}H NMR spectroscopy or gas chromatography. [c] Isolated yields. DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA=N,N-diisopropylethylamine.

For example, *N*-pentafluorophenyl substituted triazolium precatalyst **IId** exhibited superior selectivity for the cross-acyloin product **1a** with catalytic activity (Table 1, entry 5).

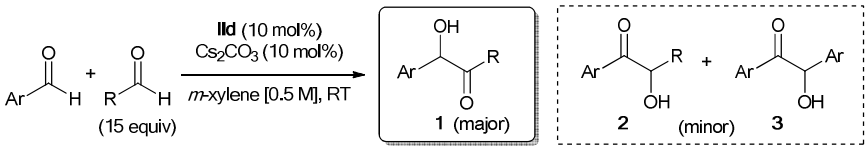
In further experiments, other reaction parameters (e.g. solvent and base) were also investigated by employing NHC precatalyst **IId**. The non-polar solvent *m*-xylene was found to be suitable for the model reaction (Table 1, entry 6). All possible adducts **1a**, **2a**, **3a** except for adduct **4a** were observed when 1.2 equivalents of isobutyraldehyde (with respect to *p*-chlorobenzaldehyde) was employed.[8]

Interestingly, the aromatic aldehyde-to-aliphatic aldehyde ratio dramatically affected the suppression of unwanted homo-acyloin adduct **3a** and the chemical yield of the specified isomer **1a**. The results with 1.2, 3, 5, 10 and 15 equivalents of isobutyraldehyde (with respect to *p*-chlorobenzaldehyde) are shown in Table 1 (entries 6-10). The highest yield was achieved when 15 equivalents of aliphatic aldehyde were used. The aromatic aldehyde-to-aliphatic aldehyde ratio is one of the most critical reaction parameters. We also screened various bases with the best NHC precatalyst **IId**. A comparable yield was obtained in the presence of DBU (Table 1, entry 11), whereas DIPEA and Et_3N were less effective in terms of chemical yield (Table 1, entries 12-13).Under the optimised reaction conditions [10 mol% of triazolium salt **IId**, 10 mol% of Cs_2CO_3, 15 equivalents of aliphatic aldehydes in *m*-xylene (0.5 M) at room temperature], a variety of aromatic and aliphatic aldehydes were investigated to examine the generality of the reaction. The results are listed in Table 2. The NHC precatalyst **IId** was applicable to virtually any aromatic aldehydes regardless of the electronic nature and the site of substituents on the aromatic ring (Table 2, entries 1-18).

Other aliphatic aldehydes were also suitable substrates for achieving high chemoselectivity (Table 2, entries 19-22 and 24-26).[9]

This is a significant improvement in display of diverse substrates and positional non-specificities in crossed acyloin condensation of aromatic aldehydes with aliphatic aldehydes. In order to reuse excessive amounts of aliphatic aldehydes, we hypothesised that further consecutive catalytic cycles may occur with the addition of an equivalent of aromatic aldehyde to the initial reaction mixture, which proved to work adequately. The detailed experimental procedure is described as follows. To a solution of *p*-chlorobenzaldehyde (0.55 mmol) and isobutyraldehyde (8.25 mmol) in 5.5 mL of dry *m*-xylene was added NHC precatalyst (10 mol%) followed by Cs_2CO_3 (10 mol%), and the suspension was stirred at room temperature for 24 h.

Table 2 Substrate scope [a]



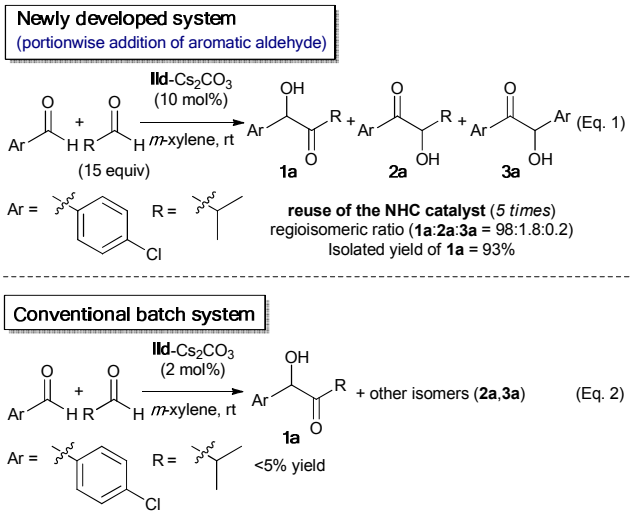
Entry	Ar / R	Ratios of **1**:**2**:**3**	Yield of **1** (%)[b]
1	4-Cl-C_6H_4 / *iso*-Propyl (**a**)	94:2:4	92
2	4-Br-C_6H_4 / *iso*-Propyl (**b**)	96:4:0	86
3	4-F-C_6H_4 / *iso*-Propyl (**c**)	97:3:0	89
4	4-CF_3-C_6H_4 / *iso*-Propyl (**d**)	82:2:16	81
5	4-Me-C_6H_4 / *iso*-Propyl (**e**)	97:3:0	61
6	3-Cl-C_6H_4 / *iso*-Propyl (**f**)	87:2:11	79
7	3-Br-C_6H_4 / *iso*-Propyl (**g**)	86:4:10	78
8	3-F-C_6H_4 / *iso*-Propyl (**h**)	87:2:11	86
9	3-CF_3-C_6H_4 / *iso*-Propyl (**i**)	80:3:17	71
10	3-CN-C_6H_4 / *iso*-Propyl (**j**)	87:2:11	86
11	3-Me-C_6H_4 / *iso*-Propyl (**k**)	98:2:0	80
12	3-MeO-C_6H_4 / *iso*-Propyl (**l**)	93:7:0	65
13	2-Cl-C_6H_4 / *iso*-Propyl (**m**)	99:1:0	98
14	2-Br-C_6H_4 / *iso*-Propyl (**n**)	92:2:6	92
15	2-F-C_6H_4 / *iso*-Propyl (**o**)	80:4:16	78
16	2-MeO-C_6H_4 / *iso*-Propyl (**p**)	98:2:0	83
17	Ph / *iso*-Propyl (**q**)	93:7:0	89
18	2-Naphthyl / *iso*-Propyl (**r**)	94:3:3	93
19	Ph / Ethyl (**s**)	94:6:0	92
20	Ph / *n*-Propyl (**t**)	90:10:0	85
21	Ph / *n*-Pentyl (**u**)	94:6:0	91
22	Ph / *n*-Hexyl (**v**)	93:7:0	92
23	Ph / *tert*-Butyl (**w**)	-	trace
24	2-Cl-C_6H_4 / Cyclohexyl (**x**)	97:3:0	93
25	3-Cl-C_6H_4 / Cyclohexyl (**y**)	88:2:10	89
26	4-Cl-C_6H_4 / Cyclohexyl (**z**)	93:2:5	85

[a] Unless otherwise specified, the reactions were performed on a 0.5-mmol scale of aromatic aldehydes with 15 equivalents of aliphatic aldehydes, 10 mol% NHC precatalysts (**IId**) and 10 mol% Cs_2CO_3 at room temperature in 5.0 mL solvent. [b] Determined by ^{1}H NMR spectroscopy or gas chromatography. [c] Isolated yields.

Upon completion of the reaction, *p*-chlorobenzaldehyde was recharged and subjected to the cross-acylion condensation under the same reaction conditions. The next cycle was performed without the addition of extra NHC catalyst.

Although the addition of substrate portions was repeated five times, the desired product was constantly obtained with the retention of chemoselectivity. Thus, the NHC catalyst demonstrated robustness and durability as it remained a catalytically active species in solution in sufficient strength to catalyse the reaction.

Percentage yield of the accumulated product (93%) was determined by dividing the amounts (591.6 mg) of the accumulated product by the theoretical yield (636.2 mg) in grams after five attempts to complete the portion-wise addition of *p*-chlorobenzaldehyde (Eq. 1, Scheme 2). No perturbations either of substrate/product or product/catalyst led to enhanced yield of the desired product **1**. A slightly better chemoselectivity was also obtained in comparison with the result in entry 1, Table 2.



Scheme 2 Discrepancy results in a comparative evaluation of two different catalytic systems with the reduced amount of NHC catalyst.

In order to compare the efficiency of the catalytic system, we performed the same reaction with 2 mol% of NHC catalyst, which was calculated by dividing the original catalyst loading (10 mol%) by repetition number (5 times). As a result, the product yield (<5 %) is abysmally low compared with our system (Eq. 2, Scheme 2). This portion-wise addition was more efficient than the corresponding one-portion experiment (2 mol%). The protocol in the present study exhibited a superior performance compared to one-off catalytic system in terms of chemoselectivity, stability, and reactivity.

Conclusions

In summary, we have developed catalytic chemoselective crossed acyloin condensation reactions of aromatic and aliphatic aldehydes without any directing group on the aromatic ring. Significantly enhanced chemoselectivity of the products was obtained by the adjustment of the aromatic-to-aliphatic aldehyde ratio. Moreover, we also demonstrated that the NHC catalyst can catalyse repeated reactions by introduction of a substantial catalyst. Further efforts to expand these concepts are ongoing in our laboratory.

Acknowledgements

This work was supported by the NRF Nano · Material Technology Development Program (2012M3A7B4049652), the KETEP Human Resources Development Program (20124010203270) and the NRF Basic Science Research Program (2009-0094023).

Notes and references

[a] Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Republic of Korea.
[b] Department of Energy Science, Sungkyunkwan University, Suwon 440-746, Republic of Korea. Fax: +82-31-299-4279; Tel: +82-31-299-4276; E-mail: jwyang@skku.edu

† Electronic Supplementary Information (ESI) available: [Experimental procedures, ^{1}H and ^{13}C NMR, IR, and HRMS spectroscopic data for all compounds **1a**-**z**]. See DOI: 10.1039/c000000x/

‡ These authors contributed equally to this work.

1 For recent reviews on green chemistry, see: (*a*) R. Noyori, *Chem. Commun*., 2005, 1807-1811; (*b*) P. G. Jessop, *Green Chem*., 2011, **13**, 1391-1398; (*c*) P. J. Dunn, *Chem. Soc. Rev*., 2012, **41**, 1452-1461; (*d*) R. A. Sheldon, *Chem. Soc. Rev*., 2012, **41**, 1437-1451.

2 For examples on the intermolecular cross-acyloin condensation reaction of two different aldehydes using NHC catalyst, see: (*a*) H. Stetter and G. Dämbkes, *Synthesis*, 1977, 403-404; (*b*) T. Matsumoto, M. Ohishi and S. Inoue, *J. Org. Chem.,* 1985, **50**, 603-606; (*c*) C. A. Rose, S. Gundala, S. J. Connon and K. Zeitler, *Synthesis*, 2011, 190-198; (*d*) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler and S. J. Connon, *J. Org. Chem*., 2011, **76**, 347-357; (*e*) M. Y. Jin, S. M. Kim, H. Han, D. H. Ryu and J. W. Yang, *Org. Lett*., 2011, **13**, 880-883; (*f*) I. Piel, M. D. Pawelczyk, K. Hirano, R. Fröhlich and F. Glorius, *Eur. J. Org. Chem*., 2011, 5475-5484; (*g*) N. Kuhl and F. Glorius, *Chem. Commun*., 2011, **47**, 573-575; Using stoichiometric amounts of triazolium salt, see: (*h*) S. M. Mennen and S. J. Miller, *J. Org. Chem.,* 2007, **72**, 5260-5269.

3 For other examples on the intermolecular cross-acyloin condensation reaction of two different carbonyl compounds using NHC catalyst, see: (*a*) D. Enders and A. Henseler, *Adv. Synth. Catal.*, 2009, **351**, 1749-1752; (*b*) D. Enders, A. Grossmann, J. Fronert and G. Raabe, *Chem. Commun*., 2010, **46**, 6282-6284; (*c*) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. franz, S. J. Connon and K. Zeitler, *Chem. Sci.*, 2012, **3**, 735-740; (*d*) K. Thai, S. M. Langdon, F. Bilodeau and M. Gravel, *Org. Lett*., 2013, **15**, 2214-2217.

4 For examples on the intermolecular cross-acyloin condensation reaction using enzyme, see: (*a*) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl and M. Müller, *J. Am. Chem. Soc*., 2002, **124**, 12084-12085; (*b*) M. Pohl, B. Lingen and M. Müller, *Chem. □ Eur. J.*, 2002, **8**, 5289-5295; (*c*) P. Lehwald, M. Richter, C. Röhr, H.-w. Liu and M. Müller, *Angew. Chem., Int. Ed*., 2010, **49**, 2389-2392; (*d*) P. Ayhan, İ. Şimşek, B. Çifçi and A. S. Demir, *Org. Biomol. Chem*., 2011, **9**, 2602-2605.

5 For comprehensive reviews on NHC catalysis, see: (*a*) D. Enders and T. Balensiefer, *Acc. Chem. Res*., 2004, **37**, 534-541; (*b*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed*., 2007, **46**, 2988-3000; (*c*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev*., 2007, **107**, 5606-5655; (*d*) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res*., 2011, **44**, 1182-1195; (*e*) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev*., 2008, **37**, 2691-2698; (*f*) E. M. Phillips, A. Chan and K. A. Scheidt, *Aldrichimica Acta,* 2009, **42**, 55-66; (*g*) J. L. Moore and T. Rovis, *Top. Curr. Chem*., 2010, **291**, 77-144.

6 For representative reviews on organocatalysis, see: (*a*) K. N. Houk and B. List, *Acc. Chem. Res.*, 2004, **37**, 487-487; (*b*) *Asymmetric Organocatalysis*, ed. A. Berkessel, H. Gröger, Wiley-VCH, Weinheim, 2005; (*c*) J. Seayad and B. List, *Org. Biomol. Chem*., 2005, **3**, 719-724; (*d*) B. List and J. W. Yang, *Science*, 2006, **313**, 1584-1586; (*e*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007; (*f*) B. List, *Chem. Rev.*, 2007, **107**, 5413-5415; (*g*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304-308; (*h*) R. C. Wende and P. R. Schreiner, *Green Chem*., 2012, **14**, 1821-1849; (*i*) J. G. Hernández and E. Juaristi, *Chem. Commun.*, 2012, **48**, 5396-5409.

7 For reviews on recycling homogeneous catalysts, see: (*a*) D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702-1706; (*b*) D. J. Cole-Hamilton and R. P. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, Springer, Dordrecht, 2006; (*c*) M. Janssen, C. Müller and D. Vogt, *Green Chem*., 2011, **13**, 2247-2257.

8 Aliphatic homo-acyloin adduct **4a** did not observed even if an excessive amount of isobutyraldehydes was used. It might result from the steric hindrance of isobutyraldehydes.

9 Relatively less hindered aliphatic aldehydes (i.e., propionaldehyde, *n*-butyraldehyde, *n*-hexaldehyde, and *n*-heptaldehyde) than isobutyraldehyde provided a small amounts of aliphatic homo-acyloin products. Individual yield of each product is as follows: i) propionaldehyde (14% yield); ii) *n*-butyraldehyde (22% yield); iii) *n*-hexaldehyde (9% yield); iv) *n*-heptaldehyde (6% yield).

