ORGANIC LETTERS

2011
Vol. 13, No. 5
880–883

Switching Regioselectivity in Crossed Acyloin Condensations between Aromatic Aldehydes and Acetaldehyde by Altering *N*-Heterocyclic Carbene Catalysts

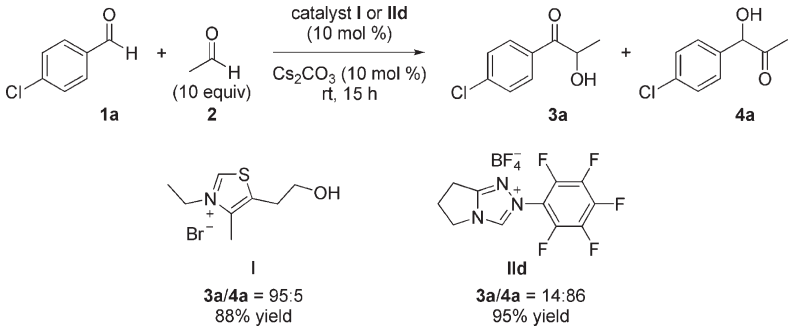
Ming Yu Jin,[†] Sun Min Kim,[‡] Hogyu Han,*[,§] Do Hyun Ryu,*[,†] and Jung Woon Yang*[,‡]

Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea, Department of Energy Science, Sungkyunkwan University, Suwon 440-746, Korea, and Department of Chemistry, Korea University, Seoul 136-701, Korea

jwyang@skku.edu; dhryu@skku.edu; hogyuhan@korea.ac.kr

Received December 4, 2010

ABSTRACT



An unprecedented high level of regioselectivities (up to 96%) in the intermolecular crossed acyloin condensations of various aromatic aldehydes with acetaldehyde was realized by an appropriate choice of *N*-heterocyclic carbene catalysts.

Carbonyl group polarity reversal is a powerful synthetic strategy that has been widely recognized in the field of carbene chemistry.[1] Originally, acyl anion catalysis stemmed from the use of thiamine-dependent enzymes. Thiamine diphosphate (ThDP)-dependent enzymes, including pyruvate decarboxylase (PDC), benzoylformate decarboxylase (BFD), and benzaldehyde lyase (BAL), have been characterized as powerful and versatile biocatalysts for the construction of carbon−carbon bonds.[2] Among them, PDC catalyzes an irreversible nonoxidative decarboxylation of pyruvate to produce an "active acetaldehyde" (2-α-hydroxyethyl-thiamine diphosphate) intermediate as an acyl anion source. In addition, its α-carbanion reacts with a variety of aldehydes through nucleophilic attack to form mixed α-hydroxy ketones with high enantioselectivities.[3]

[†] Department of Chemistry, Sungkyunkwan University.
[‡] Department of Energy Science, Sungkyunkwan University.
[§] Department of Chemistry, Korea University.

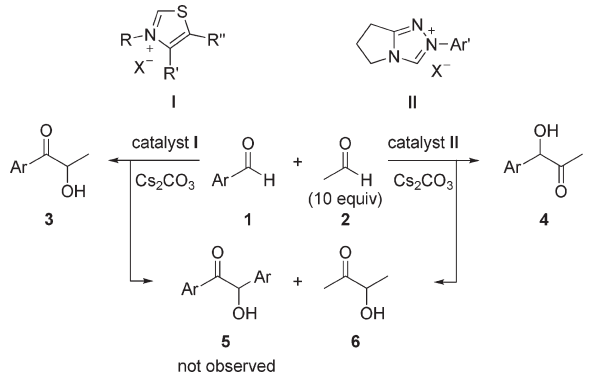
(1) For general reviews on NHC catalysts, see: (a) Enders, D.; Breuer, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 3, Ch. 30, pp 1093−1102. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541. (c) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632–2634. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510. (e) Enders, D.; Balensiefer, T.; Niemeier, O.; Christmann, M. In *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiely-VCH: Weinheim, Germany, 2007; pp 331−355. (f) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (g) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (h) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698.

(2) (a) Müller, M.; Gocke, D.; Pohl, M. *FEBS J.* **2009**, *276*, 2894–2904. (b) Pohl, M.; Sprenger, G. A.; Müller, M. *Curr. Opin. Biotechnol.* **2004**, *15*, 335–342. (c) Pohl, M.; Lingen, B.; Müller, M. *Chem.—Eur. J.* **2002**, *8*, 5288–5295.

(3) (a) Kluger, R. In *The Enzymes*, 3rd ed.; Sigman, D. S., Ed.; Academic Press: New York, 1992; Vol. 20, pp 271−315. (b) Schellenberger, A. *Angew. Chem., Int. Ed.* **1967**, *6*, 1024–1035. (c) Chen, G. C.; Jordan, F. *Biochemistry* **1984**, *23*, 3576–3582.

10.1021/ol102937w
Published on Web 01/31/2011

Scheme 1. NHC-Catalyzed Regioselective Crossed Acyloin Condensation



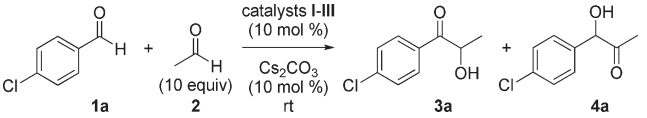
Mixed acyloin skeletons are often found as the key structural motif for many natural products with interesting biological activities and synthetic therapeutics.[4] Despite the synthetic advantages of crossed acyloin condensations between two carbonyl compounds,[5] there are two drawbacks, the undesired self-condensations and the uncontrolled regiochemistry of crossed condensations.

Given the importance of acetaldehdye as a simple nucleophile in organocatalytic reactions,[6] we hypothesized that acetaldehdye could be employed as a surrogate for an active acetaldehyde generated by a combination of pyruvate with ThDP-dependent enzymes. Such an approach can eliminate carbon dioxide emission and thus be of substantial benefit to the development of an environmentally benign process.

Here, we report a facile method for the highly regioselective crossed acyloin condensations between aromatic aldehydes **1** and acetaldehyde **2** using *N*-heterocyclic carbene (NHC) catalysts **I** and **II** (Scheme 1). It is found that the desired mixed acyloin product **3** or **4** can be obtained as a major product when the formation of self-acyloin product **5** except for acetoin **6** is suppressed by using excess acetaldehyde. In addition, we found that the control of regioselectivity in the crossed acyloin condensations of aromatic aldehydes with acetaldehyde can be achieved by properly choosing NHC catalysts.

We initiated our studies by reacting *p*-chlorobenzaldehyde **1a** with 10 equiv of acetaldehyde **2** in the presence of 10 mol % NHC (pre)catalysts and 10 mol % Cs_2CO_3 (Scheme 1 and Table 1). Fortunately, thiazolium **I** and triazolium **II** catalysts afforded the desired α-hydroxy ketones **3a**/**4a** as a mixture in high yield. Remarkably, the change of regioselectivity in such crossed reactions was accomplished by choosing between thiazolium and triazolium as a catalyst. Fortunately, thiazolium catalyst **I** was suitable for producing 1-(4-chlorophenyl)-2-hydroxypropan-1-one **3a**, whereas triazolium catalyst **II** was suitable for producing its regioisomer, 1-(4-chlorophenyl)-1-hydroxy-propan-2-one **4a**. Recently, Zeitler and Connon found that a similar regioselectivity in a crossed benzoin

Table 1. Optimization of the Reaction Conditions for NHC-Catalyzed Crossed Acyloin Condensation



entry	catalyst	solvent (M)[a]	time (h)	**3a**/**4a**[b]	yield[c] (%)
1	**I**	THF (0.5)	15	95:5	88
2	**IIa**	THF (0.3)	24	10:90	71
3	**IIb**	THF (0.3)	24	14:86	52
4	**IIc**	THF (0.5)	24	35:65	50
5	**IId**	THF (0.3)	15	17:83	91
6	**IId**	*m*-xylene (0.5)	15	14:86	95
7	**III**	THF (0.5)	24	–	–

[a] Molar concentration of 4-chlorobenzaldehyde **1a**. [b] Determined by 300 MHz ^{1}H NMR of the unpurified reaction mixture after workup. [c] Isolated yield of a **3a**/**4a** mixture obtained after flash chromatography.

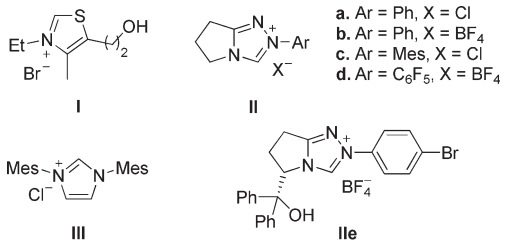


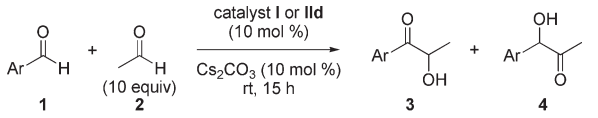
Figure 1. NHC catalysts **I**−**III** examined in this study.

(4) (a) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.-I.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052–1053. (b) Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayake, C. H.; Wald, S. A. *Tetrahedron: Asymmetry* **2000**, *11*, 3659–3663. (c) Kihumbu, D.; Stillger, T.; Hummel, W.; Liese, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1069–1072. (d) González, B.; Vicuña, R. *J. Bacteriol.* **1989**, *171*, 2401–2405. (e) Jordan, F. *Nat. Prod. Rep.* **2003**, *20*, 184–201.

(5) For a single report so far on NHC-catalyzed nonasymmetric intermolecular crossed acyloin condensations of aldehydes with ketones, see: (a) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749–1752. For NHC-catalyzed asymmetric intramolecular crossed acyloin condensations of aldehydes with ketones, see: (b) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111–2114. (c) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467. (d) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431–2434. (e) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494. (f) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263–2265. (g) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866–4869. For NHC-catalyzed nonasymmetric intramolecular crossed acyloin condensations of aldehydes with ketones, see: (h) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111–2114. (i) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433.

(6) (a) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453–455. (b) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082–2084. (c) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719–4721. (d) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722–4724. (e) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053–9058. (f) Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008**, *10*, 5581–5583. (g) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838–1840.

Table 2. NHC-Catalyzed Intermolecular Crossed Acyloin Condensations of Various Aromatic Aldehydes with Acetaldehyde[a]



a. Ar = 4-ClC$_6$H$_4$ **b.** Ar = 4-F$_3$CC$_6$H$_4$ **c.** Ar = 4-NCC$_6$H$_4$ **d.** Ar = Ph **e.** Ar = 4-MeC$_6$H$_4$ **f.** Ar = 4-MeOC$_6$H$_4$

entry	Ar	catalyst	**3**/**4**[b]	yield[c] (%)
1	4-ClC$_6$H$_4$	**I**	95:5	88
2	4-ClC$_6$H$_4$	**IId**	14:86	95
3	4-F$_3$CC$_6$H$_4$	**I**	94:6	87
4	4-F$_3$CC$_6$H$_4$	**IId**	23:77	86
5	4-NCC$_6$H$_4$	**I**	98:2	90
6	4-NCC$_6$H$_4$	**IId**	28:72	90
7	Ph	**I**	93:7	87
8	Ph	**IId**	13:87	90
9	4-MeC$_6$H$_4$	**I**	91:9	78
10	4-MeC$_6$H$_4$	**IId**	12:88	85
11	4-MeOC$_6$H$_4$	**I**	92:8	45[d]
12	4-MeOC$_6$H$_4$	**IId**	11:89	53[d]

[a] Reaction conditions: (a) ArCHO **1** (0.5 mmol), MeCHO **2** (5 mmol), catalyst **I** (0.05 mmol), Cs_2CO_3 (0.05 mmol), THF (1 mL) or (b) ArCHO **1** (0.3 mmol), MeCHO **2** (3 mmol), catalyst **IId** (0.03 mmol), Cs_2CO_3 (0.03 mmol), *m*-xylene (1 mL). [b] Determined by 300 MHz ^{1}H NMR of the unpurified reaction mixture after workup. [c] Isolated yield of a **3**/**4** mixture obtained after flash chromatography. [d] Moderate yields are due to the unreacted ArCHO starting materials rather than self-acyloin products.

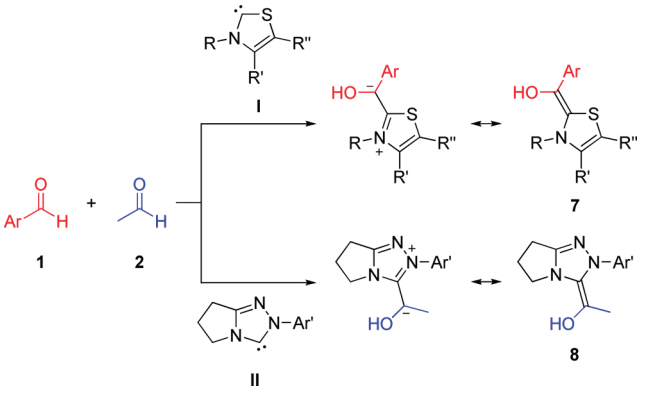
condensation between benzaldehyde and isobutyraldehyde may be achieved by employing a triazolium catalyst, but not a thiazolium catalyst.[7]

For further optimization of the reaction conditions, we investigated the effects of NHC catalysts **I**−**III**, counteranion, solvent, and concentration on the reaction of 4-chlorobenzaldehyde **1a** with acetaldehyde **2** (Table 1 and Figure 1). When thiazolium catalyst **I** was employed, an 88% yield of products **3a**/**4a** as a 95:5 mixture favoring **3a** was obtained (Table 1, entry 1). To be selective for **4a**, triazolium catalysts **II** with various *N*-substituents were employed. Regardless of *N*-substituents, all triazolium catalysts **II** afforded a **3a**/**4a** product mixture favoring **4a** (Table 1, entries 2−6). In addition, it is found that the electron-withdrawing *N*-substituent on the triazolium ring significantly increases the chemical yield. As a result, a 95% yield of products **3a**/**4a** as a 14:86 mixture favoring **4a** was obtained when triazolium catalyst **IId** with the *N*-pentafluorophenyl substituent was employed in *m*-xylene (Table 1, entry 6). The starting materials **1a** and **2** are found to remain nearly intact when treated with imidazolium catalyst **III** (Table 1, entry 7).

With these two optimized complementary reaction conditions in hand, we then explored the crossed acyloin condensation using various aromatic aldehydes with

(7) For a related study, see: O'Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2011**, *76*, 347−357.

Scheme 2. Proposed Mechanism for the NHC-Catalyzed Regioselective Crossed Acyloin Condensation

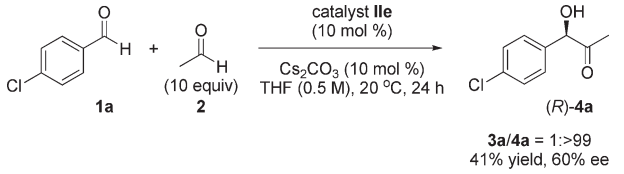


electron-withdrawing and electron-donating substituents on their aromatic ring (Table 2). First of all, thiazolium **I** and triazolium **IId** catalysts afforded a **3**/**4** product mixture predominantly favoring **3** and **4**, respectively. Regardless of the variation in the electronic properties of aromatic aldehydes, such selectivity was achieved quite effectively. Accordingly, such NHC-catalyzed crossed acyloin condensation served as an efficient and direct route for the generation of α-hydroxy ketones with excellent regioselectivity (up to 98:2) and high yield (up to 95%). In general, the chemical yield increased when electron-withdrawing substituents were introduced into aromatic aldehydes. It is noteworthy that thiazolium catalyst **I** gave superior results in terms of regioselectivity compared to triazolium catalyst **IId** in all cases.

The regioselective formation of α-hydroxy ketones **3** and **4** can be rationalized by Breslow's mechanism for the NHC-catalyzed crossed acyloin condensation (Scheme 2).[8] Nucleophilic attack of thiazolium catalyst **I** on aromatic aldehydes **1** rather than acetaldehyde **2** affords the most resonance-stabilized Breslow intermediate **7**. The nucleophilic carbene thus formed reacts with the incoming second aldehyde such as acetaldehyde and then releases the more thermodynamically stable product **3**. In contrast, nucleophilic attack of the more sterically demanding triazolium catalyst **II** on acetaldehyde **2** rather than aromatic aldehydes **1** leads to the formation of the intermediate **8**. This carbene then reacts with the second aldehyde such as aromatic aldehydes, thereby liberating the product **4**. The NHC preference for such reaction pathways may be due to the steric difference between the intermediates. For instance, there would be unfavorable steric interactions between aromatic rings if the intermediates are formed from triazolium catalyst **II** and aromatic aldehydes **1** instead of acetaldehyde **2**. Such a steric difference can critically affect their relative formation from NHC and aldehydes and their subsequent nucleophilic attack on the second aldehyde. In addition, such preference also seems to be affected

(8) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

Scheme 3. NHC-Catalyzed Asymmetric Intermolecular Crossed Acyloin Condensation



by electronic properties of aromatic aldehydes. For instance, using thiazolium catalyst **I**, the regioselectivity is better (higher **3**:**4** ratio) for electron-withdrawing substituents on the aromatic aldehydes. Using triazolium catalyst **IId**, the regioselectivity is better (higher **4**:**3** ratio) for electron-donating substituents on the aromatic aldehydes. Thus, it appears that the turnover-limiting species **7** and **8** may be favorably generated from catalysts **I** and **IId**, respectively, by the steric and electronic properties of substrates and catalysts.

Finally, we also developed an asymmetric variant of the NHC-catalyzed intermolecular crossed acyloin condensation between an aromatic aldehyde and acetaldehyde. When *p*-chlorobenzaldehyde **1a** (0.5 M in THF) reacted with 10 equiv of acetaldehyde **2** in the presence of pyroglutamic acid-derived chiral NHC catalyst **IIe** (10 mol %) at 20 °C for 24 h, α-hydroxy ketone (*R*)-**4a** was obtained with extremely high regioselectivity (> 99%) in 41% yield and 60% ee (Scheme 3).[9] We observed that no racemization of the product (*R*)-**4a** takes place under the same reaction conditions. This example demonstrated in principle that an asymmetric version of NHC-catalyzed intermolecular crossed acyloin condensation with acetaldehyde is possible in this way.

In summary, we have demonstrated for the first time the control of regioselectivity in the crossed acyloin condensations of aromatic aldehydes with acetaldehyde by properly choosing NHC catalysts. Further experimental and computational studies are ongoing and will elucidate a basis for the regiochemistry of the reactions.

Acknowledgment. This work was supported by the NRF WCU program (R31-2008-000-10029-0), the NRF grant (No. 2010-0023127), and the Faculty Research Fund (Sungkyunkwan University, 2009) to J.W.Y., the NRF Priority Research Centers Program (No. 2010-0029698) to D.H.R, and the NRF grant (No. 2010-0022070) to H.H.

Supporting Information Available. Detailed synthetic procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) The absolute configuration of the product (*R*)-**4a** was determined by comparing the sign of the optical rotation with that reported previously: synthetic (*R*)-**4a**, $[\alpha]_D^{20} = -95.2$ (*c* 0.58, MeOH) with 60% ee; lit.[10], $[\alpha]_D^{20} = -158$ (*c* 0.58, MeOH) with 98% ee.

(10) Borenenann, S.; Crout, D. H. G.; Dalton, H.; Kren, V.; Lobell, M.; Dean, G.; Thomson, N.; Turner, M. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 425–430.