Cross-Coupling Hot Paper

DOI: 10.1002/anie.201410322

Nickel-Catalyzed Dehydrogenative Cross-Coupling: Direct Transformation of Aldehydes into Esters and Amides**

*Aaron M. Whittaker and Vy M. Dong**

Abstract: *By exploring a new mode of nickel-catalyzed cross-coupling, a method to directly transform both aromatic and aliphatic aldehydes into either esters or amides has been developed. The success of this oxidative coupling depends on the appropriate choice of catalyst and organic oxidant, including the use of either α,α,α-trifluoroacetophenone or excess aldehyde. Mechanistic data that supports a catalytic cycle involving oxidative addition into the aldehyde C–H bond is also presented.*

Developing nickel catalysts for the selective oxidation of C–H bonds is an emerging strategy that overcomes the need for precious metals and enables new transformations.[1] Our laboratory has previously focused on the oxidation of aldehydes under Rh, Ru, and Co catalysis.[2] Inspired by the promise of base metals, we considered that Ni-catalyzed cross-couplings of aldehydes could be classified into three general types: redox-neutral, reductive, and oxidative (Figure 1). For example, Ogoshi's cross-coupling between two aldehydes is a redox-neutral method that generates ester bonds.[3] In comparison, reductive coupling reactions generate carbon–carbon bonds in the presence of an external reductant (e.g., Et_2Zn).[4] A complementary Ni-catalyzed cross-coupling in the presence of an external oxidant, however, represents an undeveloped mode of reactivity that warrants study.[5] Herein, we showcase a unified approach for transforming aldehyde C–H bonds into both C–O and C–N bonds using Ni-catalyzed dehydrogenative cross-couplings.[6]

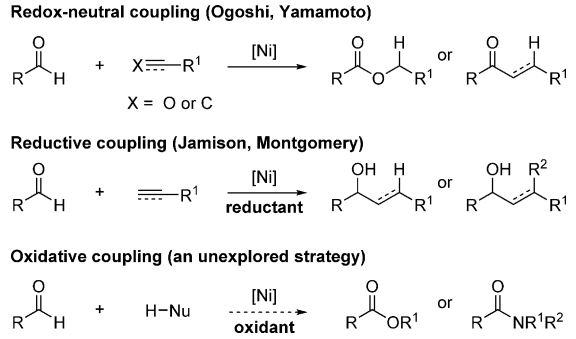
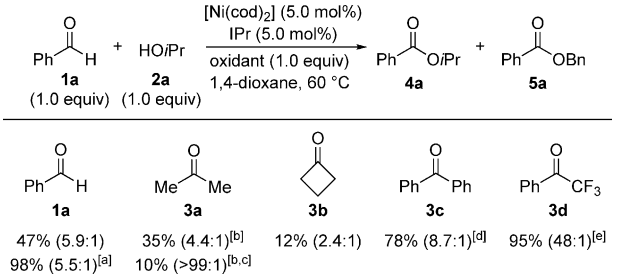


Figure 1. Three general modes for nickel-catalyzed cross-couplings with aldehydes.

The transformation of aldehydes into esters and amides in one step is an attractive goal that has been pursued using precious-metal catalysts,[7] base-metal catalysts with strong oxidants,[8] and N-heterocyclic carbene (NHC) catalysis.[9] Whereas these methods are promising, a method that couples aromatic and aliphatic aldehydes with alcohols, anilines, and amines has yet to be achieved. Towards addressing this challenge, we chose to examine carbonyl compounds as mild oxidants by hydrogen transfer.[10]

Our initial studies focused on cross-coupling benzaldehyde (**1a**) and 2-propanol (**2a**) in the presence of various hydrogen acceptors. We discovered that NHC ligands in 1,4-dioxane produced the most promising results (Scheme 1).[11]



Scheme 1. Examining organic hydrogen acceptors for oxidative esterification. Conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), 0.2 M. Yields were determined by GC analysis using dodecane as an internal standard. The yield of product **4a** is given, and the ratio of **4a**/**5a** is shown in parentheses. [a] **1a** (2.5 equiv). [b] At 80 °C. [c] **3a** (100 equiv). [d] **3c** (3 equiv). [e] At 30 °C. Bn = benzyl, cod = cyclooctadiene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene.

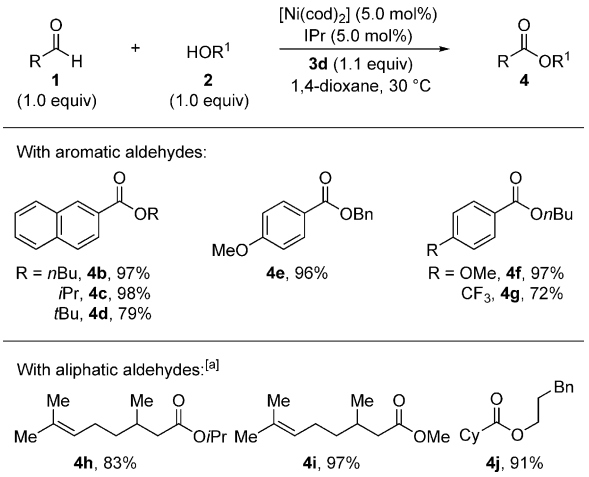
In the absence of any Ni salts, we observed no reactivity. However, in the presence of $[Ni(cod)_2]$ with benzaldehyde as both the substrate and hydrogen acceptor, we observed the formation of the desired ester **4a** and Tishchenko homodimer **5a** in a 5.9:1 ratio. To suppress the Tishchenko pathway, we sought an acceptor that undergoes reduction faster than benzaldehyde (**1a**). Whereas the addition of acetone (**3a**) and cyclobutanone (**3b**) decreased the rate of the desired cross-coupling, both benzophenone (**3c**) and α,α,α-trifluoroacetophenone (**3d**) showed a remarkable enhancement in rate and selectivity for **4a**. As a result, we were able to use equimolar quantities of the coupling partners and 1.1 equivalents of

[*] Dr. A. M. Whittaker, Prof.Dr. V. M. Dong
Department of Chemistry, University of California
Irvine, CA 92697-2025 (USA)
E-mail: dongv@uci.edu

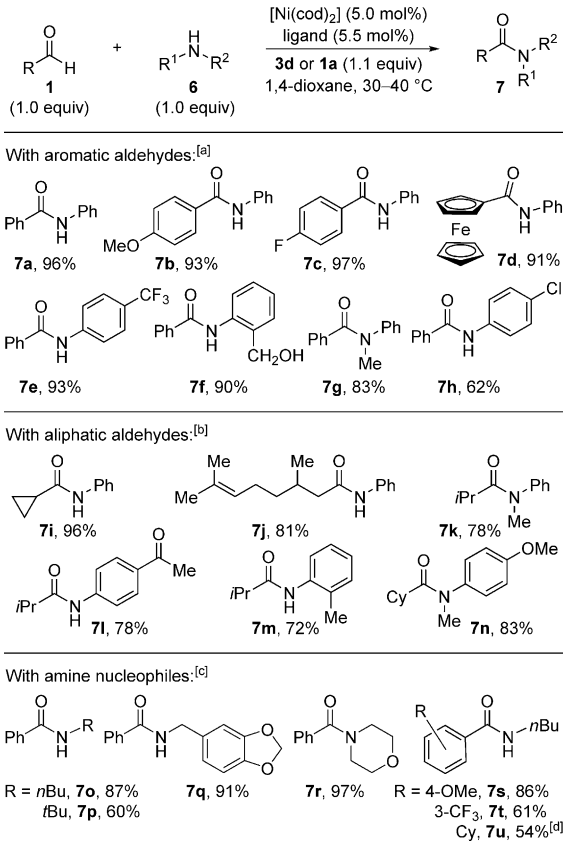
[**] Funding was provided by UC Irvine and the National Institutes of Health (GM105938). We acknowledge David George for preliminary screens with aliphatic aldehydes and Sarah Kurtoic for purification of products **7h**, **7m**, and **7n**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410322.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Dehydrogenative cross-coupling of aldehydes and alcohols. Conditions: **1** (0.5 mmol), **2** (0.5 mmol), 0.2 M, 8 h. Yields of isolated products are given. [a] Reactions performed using 10 mol% of the catalyst. Cy = cyclohexyl.



Scheme 3. Dehydrogenative cross-coupling of aldehydes and amines. Conditions: **1** (0.5 mmol), **6** (0.5 mmol), 0.2 M, 8 h. Yields of isolated products are given. [a] At 40 °C using IPr as the ligand and **3d** as the hydrogen acceptor. [b] At 30 °C using IPr as the ligand and **3d** as the hydrogen acceptor. [c] At 40 °C using I*t*Bu as the ligand and an extra equivalent of the aldehyde as the hydride acceptor. [d] Using **1a** instead of cyclohexanecarboxaldehyde as the hydrogen acceptor. I*t*Bu = 1,3-di-*tert*-butylimidazole-2-ylidene.

oxidant **3d**, with no observation of dimer **5a**. Related oxidations typically require excess alcohol,[12] or alcohol as the solvent.[13]

Under our optimized conditions, aromatic aldehydes could be coupled with primary (**4b**, 97%), secondary (**4c**, 98%) and tertiary (**4d**, 79%) alcohols at 30 °C (Scheme 2). Our method is the first intermolecular oxidative esterification to achieve high yields using only one equivalent of the tertiary alcohol nucleophile.[14] Comparatively less nucleophilic partners such as benzyl alcohol also worked well (**4e**, 96%). Both electron-rich (**4f**, 97%) and electron-deficient (**4g**, 72%) aromatic aldehydes can be transformed into esters. Whereas many NHC-catalyzed esterification reactions are limited to aromatic aldehyde substrates,[15] we found that aliphatic aldehydes undergo oxidative functionalization with Ni catalysis. Citronellal, a natural product, can be readily converted into hindered ester **4h** (83%), or methyl ester **4i** (97%). Hindered α-branched aldehydes are also well tolerated (**4j**, 91%).

In principle, couplings with amines should present a greater challenge owing to the possibility of condensation or catalyst inhibition. However, when using the same method at slightly elevated temperatures (40 °C), amide bond formation was observed using aniline nucleophiles (Scheme 3). Thus, we can convert aldehydes into amides using base-metal catalysis without relying on highly reactive reagents, such as peroxides[8] or aryl azides.[16] Under these conditions, aldehydes containing electron-donating (**7b**, 93%) or -withdrawing (**7c**, 97%) groups reacted efficiently, as well as aldehydes that would be sensitive to peroxide oxidants (**7d**, 91%).[17] Aniline nucleophiles with electron-withdrawing (**7e**, 93%) and electron-donating (**7f**, 90%) groups underwent the coupling with similar efficiency. Hindered anilines are suitable partners, including those with *ortho* substituents (**7f**, 90%) or substituents on the nitrogen atom (**7g**, 83%). Very few side products were observed in these transformations, even in the presence of an aryl chloride (**7h**, 62%).

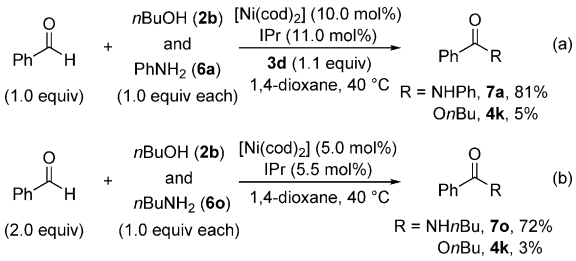
Aliphatic aldehydes are excellent coupling partners for amide synthesis (Scheme 3). At 30 °C, the reaction proceeded to full conversion with cyclopropyl carboxaldehyde without any ring opening (**7i**, 96%). β-Branching (**7j**, 81%) is well tolerated, even though pivaldehyde only provided the *N*-phenyl amide in 36% yield (not shown). An aniline with a ketone in the *para* position gives the desired amide (**7l**) in 78% yield, illustrating that ketone functional groups are tolerated despite the transfer hydrogenation nature of this reaction. The syntheses of hindered amide **7m** (72%) and tertiary amides **7k** (78%) and **7n** (83%) highlight the efficiency of this transformation.

In preliminary studies that focused on amine nucleophiles, the reactions were plagued by condensation side products. To avoid condensation with ketone **3d**, we used a second equivalent of the aldehyde as the oxidant. We were also able to suppress $[Ni(cod)_2]$ catalyzed condensation between the amine and the aldehyde by using I*t*Bu as the ligand and a Ni/ligand ratio of 1:1.1 (Scheme 3).[11] Under these conditions, the dehydrogenative coupling proceeded with primary alkyl amines (**7o**, 87%), hindered amines (**7p**, 60%), benzylic amines (**7q**, 91%), or even cyclic amines (**7r**, 97%).

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

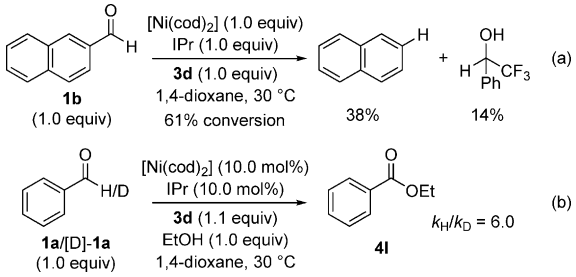
The synthesis of **7r** is a facile way to convert aldehydes into morpholine amides, which are versatile reagents for further functionalizations.[18] Amidation with amine nucleophiles is not limited to benzaldehyde substrates and can be extended to electron-rich (**7s**, 86%) or electron-poor (**7t**, 61%) aldehydes by using two equivalents of the aldehyde. Aliphatic aldehydes can also be converted into *N*-alkyl amides by using benzaldehyde as an inexpensive oxidant (**7u**, 54%).

To understand the selectivity between nucleophiles we performed a competition experiment between aniline (**6a**) and butanol (**2b**) with benzaldehyde (**1a**; Scheme 4a). The *N*-aryl amide could be formed in preference to the ester in a 16:1 ratio and 86% overall yield. Performing a similar experiment with butanol (**2b**) and *N*-butyl amine (**6o**) revealed a preference for amides in a 24:1 ratio and 72% yield with respect to *N*-butyl amine (Scheme 4b).



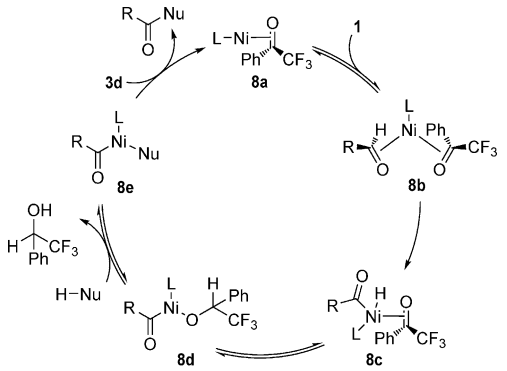
Scheme 4. Exploring the selectivity for amidation over esterification.

Towards elucidating the mechanism, we performed a stoichiometric experiment with [NiIPr], 2-naphthaldehyde (**1b**), and ketone **3d**. In this experiment, we observed reduction of the ketone and decarbonylation of the aldehyde at 30°C (Scheme 5a). This result supports the intermediacy of an acyl nickel hydride species, which can undergo decarbonylation in the absence of a coupling partner. Moreover, a KIE measurement of 6.0 suggests that C–H bond activation is rate-determining (Scheme 5b).[19]



Scheme 5. Mechanistic experiments.

On the basis of these initial studies and literature reports, we propose the mechanism shown in Scheme 6.[20] Ketone **3d** binds to nickel to form complex **8a**, which can coordinate to an aldehyde (**1**) to give intermediate **8b**. Oxidative addition to the aldehyde C–H bond generates **8c**, which reduces the hydrogen acceptor **3d** to yield acyl nickel alkoxide **8d**.[21] Ligand exchange with the nucleophile affords **8e**, and



Scheme 6. Proposed mechanism for the nickel-catalyzed dehydrogenative cross-coupling by C–H bond activation.

reductive elimination provides the final product. Coordination of ketone **3d** may occur prior to[22] or immediately after reductive elimination.[23]

Computational studies by Fu and co-workers support the concept of electron-deficient π-ligands on nickel promoting oxidative addition into aldehyde C–H bonds.[24] As empirical support for this claim we found that there was a significant increase in the reaction rate when using ketone **3d** instead of aldehyde **1a** as the hydrogen acceptor.[11] We propose that strong binding of the ketone accelerates oxidative addition.[25] This coordination also inhibits the formation of the Tishchenko side product by disrupting the formation of a cycloisomerization intermediate between two aldehydes.[26]

We have described a novel nickel-catalyzed dehydrogenative cross-coupling of aldehydes. Our method generates hindered esters and provides a needed complement to NHC-catalyzed oxidative esterification. Secondary or tertiary amides can be accessed using both aniline and amine nucleophiles in a unified approach. The discovery of **3d** as an oxidant allows cross-couplings to proceed at 30–40°C in nearly equimolar amounts of aldehyde, nucleophile, and acceptor. Future studies will include the use of Ni^{II} precatalysts[11] and nucleophiles that can result in C–C bond formation. We are also currently investigating the reaction mechanism in greater detail. Finally, the insights from this study will contribute to the expanding field of nickel-catalyzed transfer hydrogenation.[27]

Received: October 21, 2014
Published online: November 25, 2014

Keywords: amides · cross-coupling · dehydrogenation · esters · nickel

[1] For selected examples, see: a) D. Liu, C. Liu, H. Li, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 4453; *Angew. Chem.* **2013**, *125*, 4549; b) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952; c) K. Ogata, Y. Atsuumi, D. Shimada, S.-I. Fukuzawa, *Angew. Chem. Int. Ed.* **2011**, *50*, 5896; *Angew. Chem.* **2011**, *123*, 6018; d) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 5070; e) P. A. Donets, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 11772; f) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898; g) J. S.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 13098.

[2] a) K. G. M. Kou, D. N. Le, V. M. Dong, *J. Am. Chem. Soc.* **2014**, *136*, 9471; b) N. J. Oldenhuis, V. M. Dong, Z. Guan, *Tetrahedron* **2014**, *70*, 4213; c) S. K. Murphy, V. M. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 5553; d) Q. A. Chen, D. K. Kim, V. M. Dong, *J. Am. Chem. Soc.* **2014**, *136*, 3772.

[3] a) Y. Hoshimoto, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 4668; for related reactions, see: b) Y. Hoshimoto, Y. Hayashi, H. Suzuki, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2012**, *51*, 10812; *Angew. Chem.* **2012**, *124*, 10970; c) H. Taniguchi, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 11298; d) T. N. Tekavec, J. Louie, *J. Org. Chem.* **2008**, *73*, 2641; e) T. Tsuda, T. Kiyoi, T. Saegusa, *J. Org. Chem.* **1990**, *55*, 2554; f) S. Ogoshi, Y. Hoshimoto, M. Ohashi, *Chem. Commun.* **2010**, *46*, 3354.

[4] For recent reviews, see: a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; b) R. M. Moslin, K. Miller-Moslin, T. F. Jamison, *Chem. Commun.* **2007**, 4441; c) M. Kimura, Y. Tamaru, *Top. Curr. Chem.* **2007**, *279*, 173; d) H. Iida, M. J. Krische, *Top. Curr. Chem.* **2007**, *279*, 77; e) J. Montgomery, *Top. Curr. Chem.* **2007**, *279*, 1; f) J. Montgomery, *Angew. Chem. Int. Ed.* **2004**, *43*, 3890; *Angew. Chem.* **2004**, *116*, 3980.

[5] Montgomery and co-workers reported a redox-neutral Ni-catalyzed transformation of α,β-unsaturated aldehydes into methyl esters; see: a) A. Herath, W. Li, J. Montgomery, *J. Am. Chem. Soc.* **2008**, *130*, 469; Buchwald and Wolfe have noted Ni-catalyzed amide formation as a side reaction (< 26% yield) in the cross-coupling of 4-chlorobenzaldehyde and pyrrolidine; see: b) J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054.

[6] For two-step one-pot procedures that provide amides and esters, see: a) T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2013**, *15*, 5370; b) S. Iwahana, H. Iida, E. Yashima, *Chem. Eur. J.* **2011**, *17*, 8009; c) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992.

[7] For selected examples of oxidative esterification, see: a) C. Liu, S. Tang, A. Lei, *Chem. Commun.* **2013**, *49*, 1324; b) C. Liu, S. Tang, L. Zheng, D. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 5662; *Angew. Chem.* **2012**, *124*, 5760; c) C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 5144; *Angew. Chem.* **2011**, *123*, 5250; d) S. Gowrisankar, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 5139; *Angew. Chem.* **2011**, *123*, 5245; for selected examples of oxidative amidation, see: e) B. Zhou, Y. Yang, J. Shi, H. Feng, Y. Li, *Chem. Eur. J.* **2013**, *19*, 10511; f) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790; g) K. Ekoue-Kovi, C. Wolf, *Org. Lett.* **2007**, *9*, 3429; for reviews, see: h) S. Tang, J. Yuan, C. Liu, A. Lei, *Dalton Trans.* **2014**, *43*, 13460; i) H. Miyamura, S. Kobayashi, *Acc. Chem. Res.* **2014**, *47*, 1054; j) D. Milstein, *Top. Catal.* **2010**, *53*, 915; k) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* **2008**, *14*, 6302.

[8] For selected examples, see: a) L. Wang, D. L. Priebbenow, L. H. Zou, C. Bolm, *Adv. Synth. Catal.* **2013**, *355*, 1490; b) X.-F. Wu, M. Sharif, A. Pews-Davtyan, P. Langer, K. Ayub, M. Beller, *Eur. J. Org. Chem.* **2013**, 2783; c) M. Zhu, K.-I. Fujita, R. Yamaguchi, *J. Org. Chem.* **2012**, *77*, 9102; d) W.-J. Yoo, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064; for related reactions that use strong oxidants but are metal-free, see: e) Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu, X. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 3231; *Angew. Chem.* **2012**, *124*, 3285; f) K. S. Goh, C. H. Tan, *RSC Adv.* **2012**, *2*, 5536.

[9] For selected examples, see: a) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9622; *Angew. Chem.* **2014**, *126*, 9776; b) E. E. Finney, K. A. Ogawa, A. J. Boydston, *J. Am. Chem. Soc.* **2012**, *134*, 12374; c) K. Lee, H. Kim, J. Hong, *Angew. Chem. Int. Ed.* **2012**, *51*, 5735; *Angew. Chem.* **2012**, *124*, 5833; d) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; e) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; *Angew. Chem.* **2008**, *120*, 8855; f) R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick, P. M. P. Gois, *Org. Biomol. Chem.* **2011**, *9*, 3126; for oxidative amidation with NHC catalysis, see Ref. [6] and for an umpolung method employing nitroso compounds, see: g) F. T. Wong, P. K. Patra, J. Seayad, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 2333; for reviews, see: h) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; i) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664.

[10] a) B. A. Tschaen, J. R. Schmink, G. A. Molander, *Org. Lett.* **2013**, *15*, 500; b) Z. R. Dong, Y. Y. Li, S. L. Yu, G. S. Sun, J. X. Gao, *Chin. Chem. Lett.* **2012**, *23*, 533; c) G. Tang, C. H. Cheng, *Adv. Synth. Catal.* **2011**, *353*, 1918.

[11] See the Supporting Information for details.

[12] J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840; see also Ref. [7–9].

[13] R. V. Jagadeesh, H. Junge, M. M. Pohl, J. Radnik, A. Brückner, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 10776; see also Ref. [7–9].

[14] For an NHC-catalyzed method with an example of an isopropyl ester formed in good yield, see: C. Conan, L. Baragwanath, S. J. Connon, *Tetrahedron Lett.* **2008**, *49*, 4003.

[15] For a discussion of the challenges associated with aliphatic aldehydes, see: S. Kuwano, S. Harada, R. Oriez, K. Yamada, *Chem. Commun.* **2012**, *48*, 145.

[16] L. M. Jin, H. Lu, Y. Cui, C. L. Lizardi, T. N. Arzua, L. Wojtas, X. Cui, X. P. Zhang, *Chem. Sci.* **2014**, *5*, 2422.

[17] E. Baciocchi, M. Bietti, M. Di Fusco, O. Lanzalunga, *J. Org. Chem.* **2007**, *72*, 8748.

[18] R. Martín, P. Romea, C. Tey, F. Urpi, J. Vilarrasa, *Synlett* **1997**, 1414.

[19] These values are beyond the typical Claisen–Tishchenko range of 2.0–3.0; see: a) M. Sharma, T. Andrea, N. J. Brookes, B. F. Yates, M. S. Eisen, *J. Am. Chem. Soc.* **2011**, *133*, 1341; b) M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857.

[20] In the absence of a nucleophile, we observed no ketone hydroacylation, and the transformation can be performed in EtOAc as a solvent with no crossover, ruling out a mechanism involving a Tishchenko reaction followed by transesterification; see: S. P. Curran, S. J. Connon, *Org. Lett.* **2012**, *14*, 1074.

[21] In the case of amine nucleophiles, **3d** may be replaced with a second equivalent of **1a**. This is possible according to Ref. [24a] and consistent with the higher temperatures and longer reaction times.

[22] R. Giovannini, P. Knochel, *J. Am. Chem. Soc.* **1998**, *120*, 11186.

[23] J. B. Johnson, E. A. Bercot, J. M. Rowley, G. W. Coates, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 2718.

[24] a) H. Yu, Y. Fu, *Chem. Eur. J.* **2012**, *18*, 16765; for a related computational paper, see: b) S. Kozuch, S. E. Lee, S. Shaik, *Organometallics* **2009**, *28*, 1303.

[25] We did not observe decarbonylation without the ketone present; see the Supporting Information for details.

[26] S. Ogoshi, T. Arai, M. Ohashi, H. Kurosawa, *Chem. Commun.* **2008**, 1347.

[27] a) K. Nakai, Y. Yoshida, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2014**, *136*, 7797; b) P. Yang, H. Xu, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 12210; *Angew. Chem.* **2014**, *126*, 12406.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim