Homogeneous Catalysis

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A General and Mild Catalytic α-Alkylation of Unactivated Esters Using Alcohols**

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Abstract: *Catalytic α-alkylation of esters with primary alcohols is a desirable process because it uses low-toxicity agents and generates water as the by-product. Reported herein is a NCP pincer/Ir catalyst which is highly efficient for α-alkylation of a broad scope of unactivated esters under mild reaction conditions. For the first time, alcohols alkylate unactivated α-substituted acyclic esters, lactones, and even methyl and ethyl acetates. This method can be applied to the synthesis of carboxylic acid derivatives with diverse structures and functional groups, some of which would be impossible to access by conventional enolate alkylations with alkyl halides.*

α-Alkylation of esters is one of the most fundamental processes for carbon–carbon bond formation.[1] The classical methods, enolate alkylations, involve the deprotonation of the esters and the addition of the resulting enolate nucleophiles to alkyl halide electrophiles (Figure 1 a).[2] The noncatalytic S_N2 substitution reactions are presented in every introductory organic chemistry course. However, such methods have several crucial limitations: 1) the use of toxic alkylating agents and the formation of inorganic salts as waste; 2) competing side reactions, such as enolate eliminations and Claisen condensations, restrict the substrate scope (e.g., the enolates derived from methyl and ethyl acetates undergo self-condensations readily); and 3) the prerequisite formation of ester enolates typically requires harsh reaction conditions (superbase and low temperature).[1]

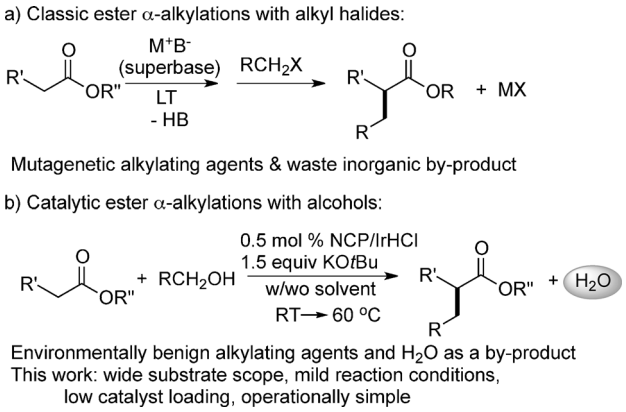

Figure 1. Classical method (a) and catalytic method (b) for α-alkylations of esters.

An alternative, but less developed method for α-alkylation of carbonyl compounds is to use alcohols as the alkylating agents. Industrially, alcohols are preferred reagents because they are more environmentally benign and less expensive than alkyl halides. Moreover, alkylations with alcohols form water as the only by-product. Over the last decade, alkylations with primary alcohols using the "borrowing hydrogen" methodology have emerged as powerful and green processes for C–C and C–N bond formations.[3] Well-developed reactions include N-alkylations of amines and sulfonamides,[3g,4] β-alkylations of alcohols (Guerbet reactions),[5] α-alkylation of ketones,[6] etc.[7]

The α-alkylation of unactivated ester with primary alcohols, however, has remained a challenging and significant goal. Recently, the group of Ishii reported the only examples of α-alkylation of unactivated ester with alcohols.[8] The reactions occurred at 100 °C in *t*BuOH with a combination of 5 mol % $[\{Ir(cod)Cl\}_2]$ and 15 mol % PPh_3 in the precense of 2 equivalents of KO*t*Bu. The work represents a breakthrough in catalytic ester alkylations, but is restricted to reactions with *tert*-butyl acetate, and a large excess of this ester (10 equiv relative to alcohol) was required.[8] *tert*-Butyl acetate is relatively easy for alkylation compared to other acetates containing smaller substituents.[1a] To the best of our knowledge, however, no catalyst systems have been reported for α-alkylations of unactivated esters other than that of *tert*-butyl acetate with alcohols.[9]

Herein we demonstrate that a pincer NCP/Ir catalyst is remarkably active for ester alkylation with primary alcohols. Most reactions proceeded to high conversion under mild reaction conditions using very low catalyst loading with alcohol to ester ratios of about 1:1 (Figure 1 b). More importantly, the protocol enables the alkylation of a wide range of esters including challenging substrates such as ethyl and methyl acetates and α-substituted esters. Furthermore, the alkylation of γ-substituted γ-butyrolactones provides *cis* α,γ-disubstituted isomers which cannot be accessed by conventional means.

We commenced by investigating iridium catalysts for alkylation of *tert*-butyl acetate (**2a**) with benzylalcohol (**1a**). Previous work in our group showed that a PN^3P pincer/Ir complex (**5**; see Table 1) catalyzes α-alkylation of unactivated secondary and tertiary acetamides with alcohols.[10] We envisioned that pincer/Ir complexes with high thermal

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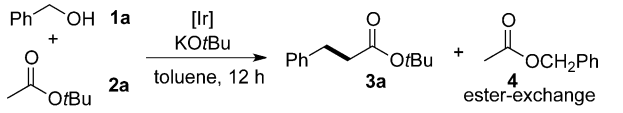
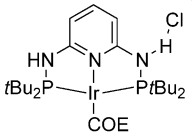
stability might be also effective for α-alkylation of unactivated esters. In a preliminary experiment, a 1:10 molar ratio of **1a**/**2a**, identical to that reported in previous study, was used.[8] Although the use of *t*BuOH as a solvent would have a beneficial effect on the reaction with *tert*-butyl acetate,[8] the ester exchange involving the solvent would limit the scope of the ester to *tert*-butyl esters. With toluene as a solvent, the reaction of **1a** with 10 equivalents of **2a** in the presence of 2 mol% of **5** and 2 equivalents of KO*t*Bu gave the alkylation product **3a** in only 25% yield after 12 hours at 110°C. The ester interchange between **1a** and **2a** formed 55% of the benzyl ester **4** as the side product (entry 1, Table 1). The

Table 1: Evaluation of iridium catalysts for α-alkylation of *tert*-butyl acetate (**1a**) with benzylalcohol (**2a**).[a]



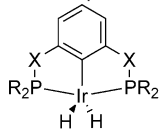
Entry	Cat. (mol%)	**2a** (equiv)	KO*t*Bu (equiv)	*T* [°C]	Yield [%][b] **3a**	**4**
1	**5** (2)	10	2	110	25	55
2	**6** (2)	10	2	110	41	39
3	**7** (2)	10	2	110	45	40
4	**8** (2)	10	2	110	78	19
5	**9** (2)	10	2	110	95	–
6	**9** (2)	10	2	60	99	–
7	**9** (0.5)	1.2	1.5	60	89 (87)	–
8	**9** (0.1)	1.2	1.5	60	68	18
9[c]	**9** (0.5)	1.2	1.5	23	86	9
10[d]	**9** (0.5)	1.2	1.5	60	72	11

[a] Reaction conditions: Ir complex (0.1–2 mol%) in 1.0 mL of toluene with **1a** (1 mmol), **2a** (1.2–10 equiv), and KO*t*Bu (1.5–2 equiv) at 60 or 110°C for 12 h. [b] Yields were determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard. Value within parentheses is the yield of the isolated product. [c] At 23°C for 3 days. [d] Reagents and solvent were used without drying, and manipulations were carried out under air.

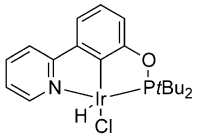


COE = cyclooctene

5



X = O, R = *t*Bu, **6**
X = CH_2, R = *t*Bu, **7**
X = CH_2, R = *i*Pr, **8**



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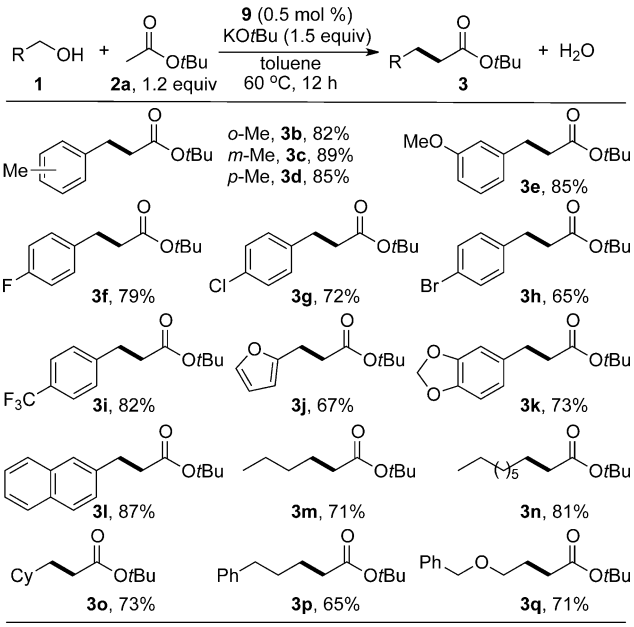
reactions using a related POCOP pincer complex (**6**) and the PCP pincer complex **7**[11] (2 mol% each) gave **3a** in 41 and 45% yields, respectively, but a decent amount of **4** was still observed (entries 2 and 3). The results indicate that the facile ester exchange is the main factor causing low conversion to the alkylation product.[12] To compete with this side reaction, the rate of iridium-catalyzed alcohol dehydrogenation to an aldehyde must be enhanced. A decrease in the steric bulk (*t*Bu groups in **7**) to the analogous complex **8** with *i*Pr groups led to an improved yield of **3a** (78%)(entry 4), thus suggesting that a less sterically hindered ligand is important for generating a more active catalyst. To this end, we investigated the NCP/Ir complex **9**. Though the electronic difference between the NCP and the classic PCP/Ir complexes remains to be studied, the replacement of one bulky di-*tert*-butyl phosphinite group in **6** with a pyridine moiety creates a sterically less demanding coordination environment around the iridium center.[13] To our delight, the reaction using **9** at 110°C gave **3a** in 95% yield, and no ester-exchange product (**4**) was observed (entry 5). The high activity of **9** allowed this transformation to occur at 60°C, thus furnishing **3a** in 99% yield after 12 h (entry 6).

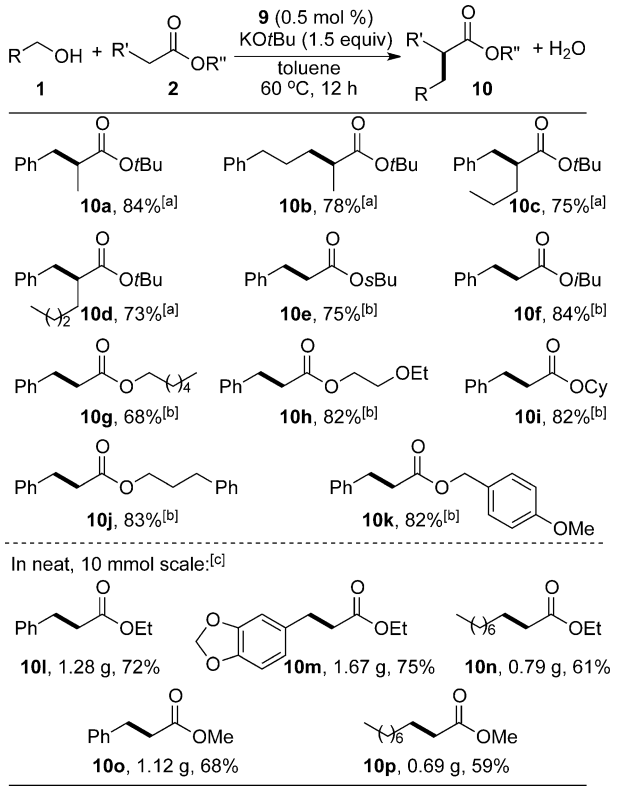
A practical catalytic alkylation should avoid using esters in large excess. With the remarkably active catalyst, we found that the reaction of **1a** with **2a** in a 1:1.2 ratio using only 0.5 mol% of **9** occurred at 60°C in high yield (Table , entry 7). The run with a lower catalyst loading (0.1 mol%) could still afford **3a** in 68% yield (entry 8). The reactions proceeded even at room temperature, thus giving **3a** in 86% yield after 3 days (entry 9). Our catalyst system is robust towards air and moisture. The reaction in the presence of air and using reagents and solvent without dyring occurred smoothly at 60°C (entry 10). Thus, the transformation can be performed without the need of a drybox, and allows the non-expert to fully utilize this methodology.

Using the very active NCP/Ir catalyst and optimal reaction conditions (entry 7, Table 1), the scope of the reaction was investigated by variying the primary alcohol (Scheme 1) and ester (Scheme 2). Benzylic alcohols contain-

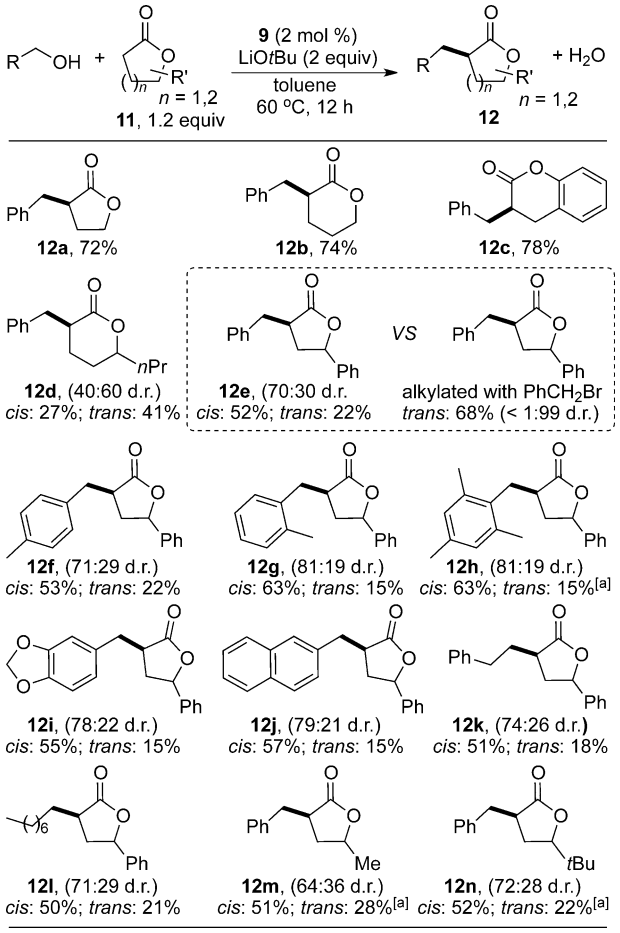


Scheme 1. NCP/Ir-catalyzed α-alkylation of *tert*-butyl acetate (**2a**) with various primary alcohols. Yields shown are of isolated products.

ing both electron-donating and electron-withdrawing groups alkylated **2a** efficiently (Scheme 1). A methyl group at all the positions on the aromatic ring was tolerated (**3b–d**). Benzylic alcohols containing *para*-fluoro, *para*-chloro, and *para*-bromo substituents were compatible (**3f–h**). No protodehalogenation products were detected under the reaction conditions. Heterocyclic alcohols, such as 2-furanmethanol (**1j**) and 1,3-benzodioxole-5-methanol (**1k**) reacted smoothly. Further-



Scheme 2. NCP/Ir-catalyzed α-alkylation of various esters with alcohols. Yields shown are those of isolated products. [a] Ester/alcohol = 1.2:1. [b] Ester/alcohol = 3:1. [c] In neat, ester/alcohol = 8:1.



Scheme 3. NCP/Ir-catalyzed α-alkylation of lactones with alcohols. Yields shown are those of isolated products. [a] Isolated as a mixture of *cis* and *trans* isomers.

more, the couplings of nonbenzylic primary alcohols (**1m–q**) and **2a** formed the desired products **3m–q** in useful yields.

More importantly, our catalyst system allows, for the first time, the α-alkylation of unactivated α-substituted esters with primary alcohols. These reactions significantly broaden the synthetic utility of this methodology. As shown in Scheme 2, the reactions of *tert*-butyl propionate, *tert*-butyl caproate, and *tert*-butyl valerate with primary alcohols in 1:1.2 ratios occurred in high yields (**10a–d**). It is well known that α-alkylation of acetates with smaller substituents is more challenging than that with *tert*-butyl acetate.[1a] Excitingly, acetates with various substituents, such as *n*-hexyl, cyclohexyl, benzyl, and 2-ethoxyethyl groups, underwent alkylation smoothly (**10e–k**), albeit with a relatively high ester to alcohol ratio (3:1). Such reactions constitute the first catalytic α-alkylation of unactivated acetates other than *tert*-butyl acetate.

Ethyl acetate is manufactured on a tremendous scale in industry for use as a low toxicity solvent. Therefore, the α-alkylation of ethyl acetate is of special interest. However, the noncatalyzed alkylation of ethyl acetate with alkyl halides is a problem because of side reactions such as the Claisen condensation.[14] Significantly, the iridium-catalyzed reactions of ethyl acetate with alcohols on a 10 mmol scale in neat (alcohol/acetate 1:8) afforded the ethyl esters **10l–n** in good yields. The most challenging substrate, methyl acetate, was alkylated on gram-scale in the same vein (**10o** and **10p**). Note that the unreacted volatile acetates could be easily separated from the products through distillation and reused thereafter. Thus, the protocol provides a simple and clean approach to ethyl and methyl esters by utilizing the low-cost, low-toxicity, and readily accessible acetate sources.

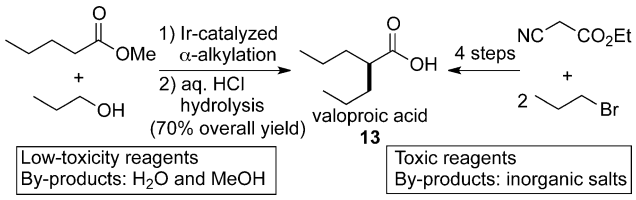
The successful α-alkylation of α-substituted acyclic esters (**10a–d**; Scheme 2) inspired us to develop procedures for catalytic the α-alkylation of lactones. As summarized in Scheme 3, the reactions of the γ-butyrolactone (**11a**; 1.2 equiv) with **1a** in the presence of 0.5 mol% **9** and 2 equivalents LiO*t*Bu at 60°C afforded the α-alkylation product **12a** in 72% yield.[15] δ-Valerolactone (**11b**) and dihydrocoumarin (**11c**), which have six-membered rings, also underwent α-alkylation smoothly. The alkylation of (*R*,*S*)-δ-octalactone (**11d**) with **1a** gives a 40:60 mixture of the *cis* and *trans* diastereomers. The reaction of (*R*,*S*)-γ-phenyl-γ-butyrolactone (**11e**) formed **12e** with a 70:30 d.r. Of significance is the isolation of the *cis* α,γ-disubstituted γ-butyrolactone (52% isolated yield) as the major product because the *cis* isomer cannot be prepared by traditional enolate alkylation with an alkyl halide.[16] For instance, the alkylation of **11e** with benzyl bromide and LDA at −78°C formed the thermodynamically more stable *trans* isomer exclusively.

A range of benzylic and nonbenzylic alcohols reacted with γ-butyrolactones to give the *cis* products diastereoselectively

(**12f–n**; Scheme 3). The incorporation of an *ortho* substituent on the benzylalcohols leads to enhanced selectively (81:19 d.r. for **12g** and **12h**). The size of the substitutents at the γ position of the γ-butyrolactones has a minor impact on the selectivity (70:30 for **12e** versus 64:36 for **12m**, and 72:28 for **12n**). Although the diastereoselectivity is moderate (up to 81:19 d.r.), this is an effective asymmetric method for the synthesis of *cis* α,γ-disubstituted butyrolactones.

We attribute the preference for the formation of the *cis* diastereomers to the iridium-catalyzed asymmetric hydrogenation of α,β-unsaturated carbonyl intermediate with diastereotopic faces. The iridium center would preferably attack the less sterically demanding face (*trans* to the γ-substituent), and the subsequent addition of hydrogen to the C–C double bond in a *cis* fashion leads to the formation of the *cis* products.

Finally, the method was applied to a convenient synthesis of an important anticonvulsant drug, valoproic acid (**13**). The current synthesis of **13** begins with the dialkylation of cyanoacetate with mutagenic *n*-propyl bromide, followed by a multiple-step hydrolysis and decarboxylation (at 140–190 °C) sequence (Scheme 4).[17] The process gives a significant amount of inorganic salts as by-products. By comparison,



Scheme 4. Catalytic and classical methods for synthesis of valoproic acid (**13**).

the catalytic method reported herein allows a short, mild, and clean synthesis of **13** from inexpensive and low-toxicity reagents. With *n*-propanol (8 mL) as the alkylating reagent/solvent, the reaction of methyl valerianate (10 mmol) in the presence of 0.5 mol% of an iridium catalyst at 60 °C formed valoproic esters. Following hydrolysis, **13** was obtained on a gram-scale in two steps and 70% overall yield (1.0 g), with H_2O and MeOH as the by-products (Scheme 4).

In summary, we have developed an effective method for α-alkylation of unactivated esters with primary alcohols by using an NCP/Ir pincer complex. The new method overcomes several limitations and complements the scope of current methods for ester alkylation. Featuring mild reaction conditions, environmentally benign reagents, broad substrate scope, good functional group compatibility, and high atom economy with water as the by-product, this method is a simple, practical, and green process for α-alkylation of esters.

Keywords: alcohols · alkylation · homogeneous catalysis · iridium · synthetic methods

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Angew. Chem. **2015**, *127*, 4095–4099

[1] a) F. A. Carey, R. K. Sundberg in *Advanced Organic Chemistry*, 5th ed., Part B, Springer, Heidelberg, **2007**, pp. 1–31; b) J. Hoyle in *The Chemistry of Acid Derivatives*, *Vol. 2* (Ed.: S. Patai), Wiley, Chichester, UK, **1992**, pp. 615–702.

[2] For examples, see: a) S. Danishefsky, K. Vaughan, R. Gadwood, K. Tsuzuki, *J. Am. Chem. Soc.* **1981**, *103*, 4136; b) T. Ling, C. Chowdhury, B. A. Kramer, B. G. Vong, M. A. Palladino, E. A. Theodorakis, *J. Org. Chem.* **2001**, *66*, 8843; c) A. Zakarian, A. Batch, R. A. Holton, *J. Am. Chem. Soc.* **2003**, *125*, 7822.

[3] For reviews, see: a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 249; b) R. H. Crabtree, *Organometallics* **2011**, *30*, 17; c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853; d) T. Suzuki, *Chem. Rev.* **2011**, *111*, 1825; e) Y. Obora, Y. Ishii, *Synlett* **2011**, 30; f) O. Saidi, J. M. J. Williams, *Iridium Catal.* **2011**, *34*, 77; g) A. J. A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635; h) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611; i) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681; j) K.-i. Fujita, R. Yamaguchi, *Synlett* **2005**, 560.

[4] For examples, see: a) C. Gunanathan, D. Milstein, *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; *Angew. Chem.* **2008**, *120*, 8789; b) F. Shi, M. K. Tse, S. Zhou, M.-M. Pohl, J. Radnik, S. Hübner, K. Jähnisch, A. Brückner, M. Beller, *J. Am. Chem. Soc.* **2009**, *131*, 1775; c) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766; d) S. Michlik, R. Kempe, *Chem. Eur. J.* **2010**, *16*, 13193.

[5] For examples, see: a) C. S. Cho, B. T. Kim, H.-S. Kim, T.-J. Kim, S. C. Shim, *Organometallics* **2003**, *22*, 3608; b) T. Matsu-ura, S. Sakaguchi, Y. Obora, Y. Ishii, *J. Org. Chem.* **2006**, *71*, 8306; c) R. Martínez, D. J. Ramón, M. Yus, *Tetrahedron* **2006**, *62*, 8982; d) L. J. Allen, R. H. Crabtree, *Green Chem.* **2010**, *12*, 1362.

[6] For examples, see: a) C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim, *Tetrahedron Lett.* **2002**, *43*, 7987; b) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2004**, *126*, 72; c) T. Kuwahara, T. Fukuyama, I. Ryu, *Org. Lett.* **2012**, *14*, 4703; d) M. L. Buil, M. A. Esteruelas, J. Herrero, S. Izquierdo, I. M. Pastor, M. Yus, *ACS Catal.* **2013**, *3*, 2072; e) Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou, J. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 225; *Angew. Chem.* **2014**, *126*, 229; f) L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2014**, *53*, 761; *Angew. Chem.* **2014**, *126*, 780; g) S. Ogawa, Y. Obora, *Chem. Commun.* **2014**, *50*, 2491.

[7] Selected examples of other types of C–C and C–N bond formations by dehydrogenative alcohol activations, see: a) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, Y.-M. Zhao, W.-J. Xia, *J. Am. Chem. Soc.* **2005**, *127*, 10836; b) S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* **2007**, *9*, 3299; c) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790; d) J. F. Bower, E. Skucas, R. L. Patman, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 15134; e) B. Blank, R. Kempe, *J. Am. Chem. Soc.* **2010**, *132*, 924; f) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140; g) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 597; *Angew. Chem.* **2013**, *125*, 625.

[8] Y. Iuchi, Y. Obora, Y. Ishii, *J. Am. Chem. Soc.* **2010**, *132*, 2536.

[9] For examples of the α-alkylation of activated esters, see: a) P. J. Black, G. Cami-Kobeci, M. G. Edwards, P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Org. Biomol. Chem.* **2006**, *4*, 116; b) M. Morita, Y. Obora, Y. Ishii, *Chem. Commun.* **2007**, 2850; c) R. Grigg, C. Lofberg, S. Whitney, V. Sridharan, A. Keep, A. Derrick, *Tetrahedron* **2009**, *65*, 849.

[10] a) L. Guo, Y. Liu, W. Yao, X. Leng, Z. Huang, *Org. Lett.* **2013**, *15*, 1144. More recently, Ryu et al. reported ruthenium-catalyzed α-alkylation of unactivated tertiary acetamides. See: b) T. Kuwahara, T. Fukuyama, I. Ryu, *RSC Adv.* **2013**, *3*, 13702.

[11] These iridium pincer complexes have been well studied for alkane hydrogenations. For a recent review, see: J. Choi, A. H. R. MacArthur, M. Brookhart, A. S. Goldman, *Chem. Rev.* **2011**, *111*, 1761.
[12] The ester interchange occurs in the absence of the iridium catalyst. Under otherwise identical reactioin conditions, the reaction without the iridium catalyst gave **4** in 24% yield after 1 h.
[13] We recently reported the NCP pincer/Ir complex for transfer dehydrogenation of alkanes. See: X. Jia, L. Zhang, C. Qin, X. Leng, Z. Huang, *Chem. Commun.* **2014**, *50*, 11056.
[14] As a comparison, the reaction of ethyl acetate with lithium diisopropylamide and benzyl bromide at −78 °C gave only 17% of the alkylation product **101**.
[15] The reaction with 2 equiv of Li*O*t*Bu provided higher yield than that with 1.5 equiv of K*O*t*Bu (53% yield).
[16] Ghosh et al. demonstrated the selective formation of *trans* α,γ-disubstituted butyrolactones through alkylation with various alkyl halides. See: A. K. Ghosh, K. Shurrush, S. Kulkarni, *J. Org. Chem.* **2009**, *74*, 4508.
[17] a) M. Chignac, C. Grain, U.S. Pat. 4155929, **1979**; b) H. E. J.-M. Meunier, U.S. Pat. 3325361, **1967**.

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