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Palladium-catalyzed decarboxylative acylation of *O*-methyl ketoximes with α-keto acids†

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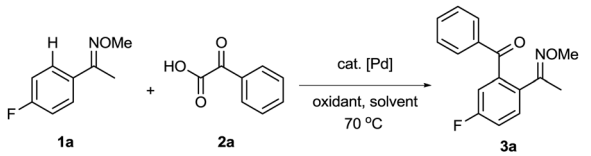
A mild, practical and efficient palladium-catalyzed decarboxylative *ortho*-acylation of *O*-methyl ketoximes with α-keto acids *via* C–H bond activation is described. In these reactions, a broad range of *O*-methyl ketoximes and α-keto acids undergoes the decarboxylative cross-coupling reactions with high selectivities and good tolerance.

Aryl ketones are important structural motifs found in natural products, medicinally relevant molecules, and functional materials.[1] In particular, 1,2-diacylbenzenes are known to be crucial synthetic precursors to construct a wide range of biologically active compounds including phthalazines, phthalimidines, isobenzofuranes, indanones, isoindoles, and isoindolines.[2] These facts have led to increasing interest in developing an efficient method for the preparation of 1,2-diacylbenzenes. Traditional metal-catalyzed cross-coupling reactions between aryl metal reagents and aryl halides are well-established methods for carbon–carbon bond formations.[3] Recently, transition-metal-catalyzed decarboxylative cross-coupling reactions using aryl carboxylic acids as coupling partners have emerged as a promising set of carbon–carbon bond formation reactions.[4] In these reactions, readily available carboxylic acids enable decarboxylative cross-coupling reactions to proceed with high selectivities and tolerance of functional groups. Therefore, decarboxylative cross-coupling reactions provide new alternatives for Mirozoki–Heck type reactions,[5] oxidative arylation,[6] redox-neutral biaryls synthesis,[7] and allylation.[8] Recently, directing-group-assisted activation of aromatic *ortho*-C–H bonds, and subsequent acylation reaction by coupling with aldehydes or alcohols have been reported.[9] A variety of directing groups, such as pyridines,[10] amides,[11] oximes,[12] acetanilides,[13] and indole,[14] have been used for C–H bond activation. However, decarboxylative acylations of aromatic C–H bonds using α-keto acids as acyl surrogates were relatively unexplored. Goossen *et al.* first demonstrated a Pd-catalyzed decarboxylative acylation of aryl bromides with α-keto carboxylate salts as acyl anion equivalents to afford diaryl ketones.[15] Ge *et al.* described palladium-catalyzed decarboxylative *ortho*-acylations of acetanilides and phenylpyridines with α-keto acids as acyl sources *via* C–H bond activation.[16] Recently, Guo and Duan *et al.* reported a decarboxylative acylation of the sp^2 C–H bond in cyclic enamides with α-keto acids.[17]

Oximes are common protection groups of the ketone moiety, and frequently used as directing groups in C–H bond activation protocols.[18] Our continued efforts in transition-metal-catalyzed C–H bond activation and oxidative acylation reactions[11] prompted us to explore the reaction of *O*-methyl ketoximes with α-keto acids. In our initial study, 4-fluoroacetophenone *O*-methyl oxime (**1a**) and phenylglyoxylic acid (**2a**) were chosen as model substrates for optimizing the reaction conditions, and selected results are summarized in Table 1.

To our delight, the combination of $Pd(OAc)_2$ and ammonium persulfate in DCE solvent at 70 °C can catalyze the coupling of **1a**

Table 1 Selected optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	DCE	32
2	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	Toluene	12
3	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	THF	37
4	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	DMF	10
5	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	Diglyme	45
6[c]	**$Pd(OAc)_2$**	**$(NH_4)_2S_2O_8$**	**Diglyme**	**72**
7[c]	$Pd(TFA)_2$	$(NH_4)_2S_2O_8$	Diglyme	61
8[c]	$Pd(PPh_3)_2Cl_2$	$(NH_4)_2S_2O_8$	Diglyme	27
9[c]	$Pd_2(dba)_3$	$(NH_4)_2S_2O_8$	Diglyme	0
10[c]	$Pd(OAc)_2$	$K_2S_2O_8$	Diglyme	41
11[c]	$Pd(OAc)_2$	Ag_2O	Diglyme	Trace
12[d]	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	Diglyme	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd catalyst (10 mol%), oxidant (0.45 mmol), solvent (1 mL) for 20 h in pressure tubes. [b] Isolated yields by flash column chromatography. [c] 3 h. [d] Room temperature, 20 h.

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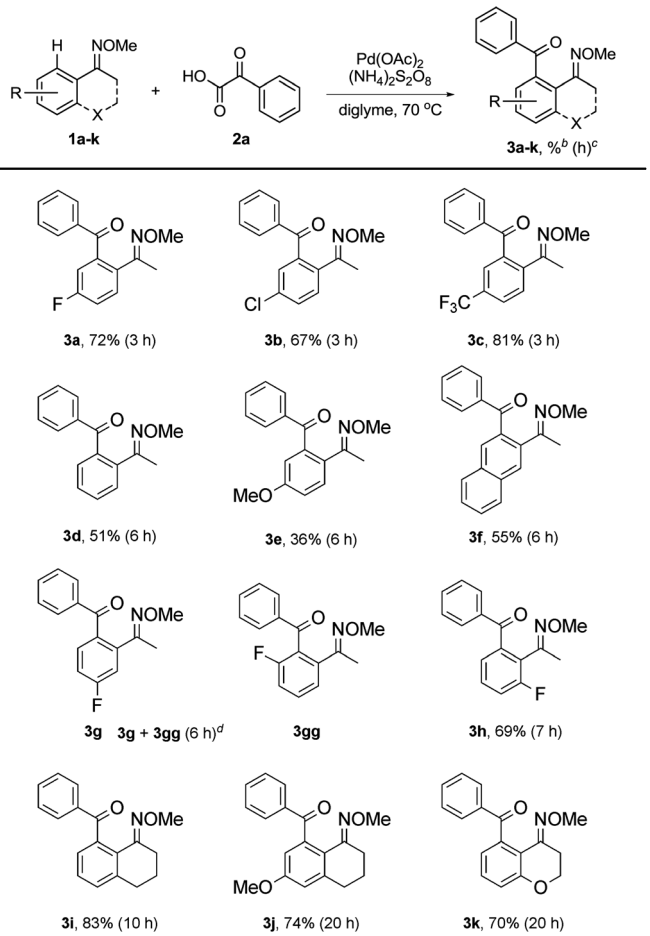
and **2a** to provide an acylated product **3a** in 32% yield. Further screening of solvents showed that diglyme is superior to other solvents such as toluene, THF, and DMF (Table 1, entries 2–5). Interestingly, we found that the coupling reaction between **1a** and **2a** was completed within 3 h under otherwise reaction conditions by TLC monitoring, affording our desired product **3a** in 72% yield (Table 1, entry 6). Thus, we believe that the longer reaction times lead to a decrease in chemical yield presumably due to the decomposition of the product under these reaction conditions. As shown in entries 7–11, a range of Pd catalysts and oxidants was tested under the identical reaction conditions, but $Pd(OAc)_2$ and $(NH_4)_2S_2O_8$ were found to be best among the other catalysts and oxidants, respectively. However, this coupling reaction did not proceed at room temperature, even for longer reaction time (Table 1, entry 12).

Under the optimized reaction conditions, the reactivity of different *O*-methyl ketoximes was investigated (Table 2). The coupling of acetophenone *O*-methyl oximes **1b–1d** with electron-neutral and withdrawing groups at the *para*-position underwent smoothly the acylation reaction to afford the corresponding products **3b–3d** in moderate to high yields. However, a strong electron donating group (OMe) at the *para*-position of acetophenone *O*-methyl ketoximes gave a lower yield of decarboxylative coupling product **3e**. The acylation reaction of 2-acetonaphthone *O*-methyl oxime (**1f**) occurred exclusively at the less sterically hindered position. However, fluoro-substituted ketoxime **1g** at the *meta*-position furnished the acylated product **3g**, albeit providing the regioisomers at C_6 and C_2 with 2 : 1 ratio. These data suggest that the steric effect of the substrates strongly interferes with either the formation of the cyclopalladated intermediate or the proximity of α-keto acid into the cyclopalladated intermediate. Pleasingly, *ortho*-substituted ketoximes **1h–1k** were found to be good substrates for this transformation, affording the corresponding products **3h–3k**.

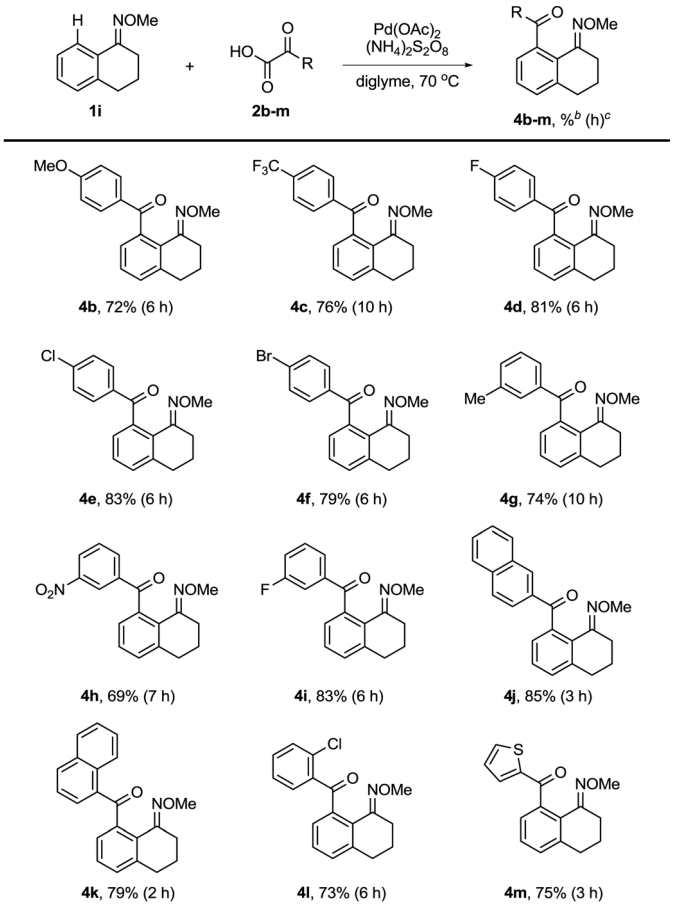
To examine the substrate scope and limitations, a broad range of α-keto acids were screened to couple with tetralone *O*-methyl oxime **1i** under optimal reaction conditions (Table 3). With either electron-rich or electron-deficient groups, for example *p*-MeO (**2b**), *m*-Me (**2g**), *p*-CF_3 (**2c**), and *m*-NO_2 (**2h**) groups, the decarboxylative coupling reactions underwent smoothly in high yields. This transformation also showed good tolerance toward the halogen groups. Notably, the chloro and bromo groups offer versatile synthetic functionality for further elaborations of the products using other traditional cross-coupling reactions.

Table 2 Scope of *O*-methyl ketoximes[a]

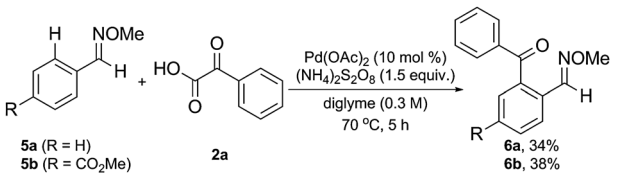


[a] Reaction conditions: **1a–k** (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (0.45 mmol), diglyme (1 mL) in sealed tubes. [b] Yield isolated by flash column chromatography. [c] Reaction time in hours. [d] Regioisomers **3g** and **3gg** were obtained with 2 : 1 ratio.

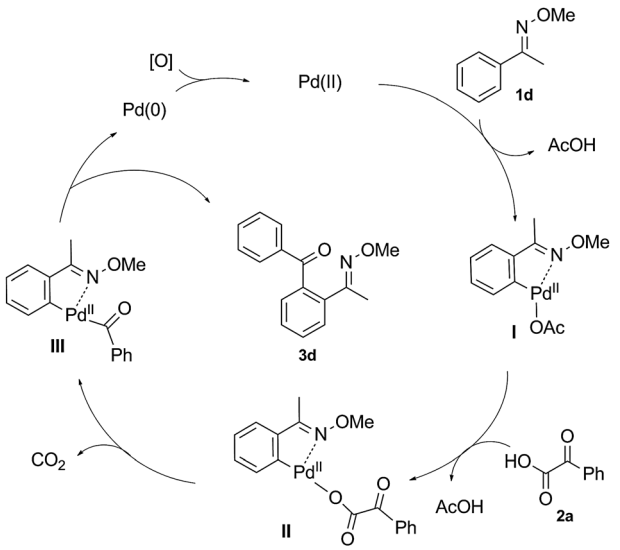
Table 3 Scope of α-keto acids[a]



[a] Reaction conditions: **1i** (0.3 mmol), **2b–m** (0.45 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (0.45 mmol), diglyme (1 mL), 70 °C in sealed tubes. [b] Yield isolated by flash column chromatography. [c] Reaction time in hours.



Scheme 1 Expansion of substrate scope from ketoximes to aldoximes.



Scheme 2 Postulated reaction mechanism.

Meanwhile, α-keto acids **2j** and **2k** with the naphthyl moiety also participated in the acylation process with a high reactivity. Finally, *ortho*-substituted phenylglyoxylic acid and heterocyclic α-keto acid were also found to be favored under this catalytic system to afford the corresponding products **4l** and **4m** in high yields.

To evaluate the scope of present catalytic reaction, we expanded our substrate scope from ketoximes to aldoximes (Scheme 1). To our pleasure, benzaldehyde *O*-methyl oximes with electron-neutral and withdrawing substituents (**5a** and **5b**) were coupled with phenylglyoxylic acid (**2a**) under the above optimal conditions, albeit in slightly decreased reactivity. Further detailed optimizations for the coupling of aldoximes and α-keto acids are in progress.

Although a reaction mechanism is not clear at this stage, it is believed that this transformation begins with the *ortho*-palladation of acetophenone *O*-methyl oxime (**1d**) with $Pd(OAc)_2$ to provide the 5-membered palladacycle **I**, which can be subsequently reacted with α-keto acid to afford cyclopalladated complex **II** (Scheme 2). Decarboxylation of cyclopalladated complex **II** followed by reductive elimination provides our desired product **3d**. Finally, the regenerated Pd(0) catalyst can be reoxidized to the active Pd(II) catalyst with $(NH)_4S_2O_8$. Although our proposed reaction mechanism is based on Pd(0) and Pd(II) catalytic cycles, the alternative reaction mechanisms including Pd(II/III)[19] and/or Pd(II/IV)[20] catalytic cycles are also reasonable to consider under strong oxidation conditions.

In summary, we described a Pd-catalyzed decarboxylative *ortho*-acylation of *O*-methyl ketoximes with α-keto acids under ammonium persulfate as a convenient oxidant *via* C–H bond activation. The ongoing studies seek to gain further insight into the coupling reactions using other directing groups and to expand the scope to the decarboxylative acylation of sp^2 C–H bonds without directing groups and unactivated sp^3 C–H bonds.

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Notes and references

1 (*a*) H. Surburg and J. Panten, *Common Fragrance and Flavor Materials*, Wiley-VCH, Weinheim, Germany, 5th edn, 2006; (*b*) Y. Deng, Y.-W. Chin, H. Chai, W. J. Keller and A. D. Kinghorn, *J. Nat. Prod.*, 2007, **70**, 2049; (*c*) K. R. Romins, G. A. Freeman, L. T. Schaller, J. R. Cowan, S. S. Gonzales, J. H. Tidwell, C. W. Andrews, D. K. Stammers, R. J. Hazen, R. G. Ferris, S. A. Short, J. H. Chan and L. R. Boone, *J. Med. Chem.*, 2006, **49**, 727; (*d*) P. J. Masson, D. Coup, J. Millet and N. L. Brown, *J. Biol. Chem.*, 1994, **270**, 2662.
2 A. Kotali and P. A. Harris, *Org. Prep. Proced. Int.*, 2003, **35**, 583.
3 (*a*) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177; (*b*) A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004; (*c*) N. Miyaura, *Cross-Coupling Reactions: A Practical Guide*, Springer, Berlin, 2004.
4 For recent reviews, see: (*a*) J. Cornella and I. Larrosa, *Synthesis*, 2012, 653; (*b*) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030.
5 For selected examples, see: (*a*) Z. Fu, S. Huang, W. Su and M. Hong, *Org. Lett.*, 2010, **12**, 4992; (*b*) P. Forgione, M. C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey and F. Bilodeau, *J. Am. Chem. Soc.*, 2006, **128**, 11350; (*c*) A. G. Myers, D. Tanaka and M. R. Mannion, *J. Am. Chem. Soc.*, 2002, **124**, 11250.
6 For selected examples, see: (*a*) F. Zhang and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 2768; (*b*) C. Wang, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 4194.
7 For selected examples, see: (*a*) L. J. Goossen, N. Rodriguez and C. Linder, *J. Am. Chem. Soc.*, 2008, **130**, 15248; (*b*) L. J. Goossen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662.
8 J. Wang, Z. Cui, Y. Zhang, H. Li, L.-M. Wu and Z. Liu, *Org. Biomol. Chem.*, 2011, **9**, 663.
9 For a recent review on catalytic acylation of sp^2 C–H bonds, see: C. Pan, X. Jia and J. Cheng, *Synthesis*, 2012, 677.
10 (*a*) X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (*b*) O. Baslé, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; (*c*) F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng and C.-J. Li, *Org. Lett.*, 2011, **13**, 1614.
11 (*a*) J. Park, E. Park, A. Kim, Y. Lee, K.-W. Chi, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Lett.*, 2011, **13**, 4390; (*b*) S. Sharma, E. Park, J. Park and I. S. Kim, *Org. Lett.*, 2012, **14**, 906.
12 (*a*) C.-W. Chan, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.*, 2010, **12**, 3926; (*b*) Y. Yang, B. Zhou and Y. Li, *Adv. Synth. Catal.*, 2012, **354**, 2916.
13 (*a*) Y. Wu, B. Li, F. Mao, X. Li and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 3258; (*b*) C.-W. Chan, Z. Zhou and W.-Y. Yu, *Adv. Synth. Catal.*, 2011, **353**, 2999; (*c*) C. Li, L. Wang, P. Li and W. Zhou, *Chem.–Eur. J.*, 2011, **17**, 10208.
14 B. Zhou, Y. Yang and Y. Li, *Chem. Commun.*, 2012, **48**, 5163.
15 L. J. Goossen, F. Rudolphi, C. Oppel and N. Rodríguez, *Angew. Chem., Int. Ed.*, 2008, **47**, 3043.
16 (*a*) P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898; (*b*) M. Li and H. Ge, *Org. Lett.*, 2010, **12**, 3464.
17 H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.*, 2012, **14**, 4358.
18 For recent selected examples, see: (*a*) T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 11846; (*b*) A. S. Tsai, M. Brasee, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2011, **13**, 540; (*c*) V. S. Thirunavukkarasu and C.-H. Cheng, *Chem.–Eur. J.*, 2011, **17**, 14723.
19 D. C. Power, M. A. L. Geibel, J. E. M. N. Klein and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 17050.
20 (*a*) C. F. Rosewall, P. A. Sibbald, D. V. Liskin and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 9488; (*b*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945.