ORGANIC LETTERS

2011
Vol. 13, No. 3
422−425

Palladium-Catalyzed Cross-Coupling of Indium Homoenolate with Aryl Halide with Wide Functional Group Compatibility

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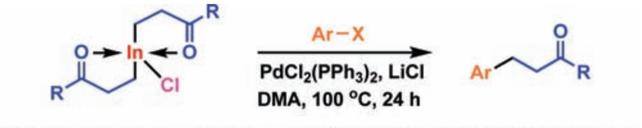
Received November 13, 2010

ABSTRACT



Wide functional group tolerance: COR, COOR, CHO, CN, NO_2, OH, *etc.*

An efficient palladium-catalyzed cross-coupling of indium homoenolate with aryl halide is described. The reactions proceeded efficiently in DMA at 100 °C to afford the desired products of *β*-aryl ketones in moderate to good yields. Various important functional groups including COR, COOR, CHO, CN, OH, and NO_2 can be well tolerated in the protocol.

Transition-metal-catalyzed cross-coupling of organometallic reagents with various electrophiles constitutes one of the most important methods for the construction of the C−C bond.[1] Among the various organometallic reagents developed, organoindium reagents, because of their wide compatibility with various functional groups such as hydroxyl, carbonyl, and even water,[2−8] have emerged as an important alternative to other reactive organometallic species such as organomagnesium and organozinc reagents. The first cross-coupling of an organoindium reagent with an aryl halide was pioneered by Sarandeses employing a triorganoindium reagent (R_3In, prepared via transmetalation of RLi or RMgX with $InCl_3$) in THF.[9,10] Recently, Knochel,[2,3] Minehan,[4] Chupak,[5] and Yamamoto[6] have reported efficient methods for the direct syntheses of benzyl and/or aryl indium reagents from organohalides and their applications in palladium-catalyzed cross-coupling with aryl halides.

More recently, our group[8] has reported an efficient method for the synthesis of water-tolerant, ketone-type indium homoenolate[11−13] via oxidative addition of an indium(I) reagent to enone in aqueous media, and the synthetic utility of the indium homoenolate was demonstrated by the synthesis of a 1,4-dicarbonyl compound via palladium-catalyzed coupling with acid chloride in THF. In continuation of our further efforts in developing the synthetic utility of the indium homoenolate in organic synthesis, we aimed at achieving the transition-metal-catalyzed cross-coupling of the

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(2) Chen, Y. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 7648.

(3) Chen, Y. H.; Sun, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 2236.

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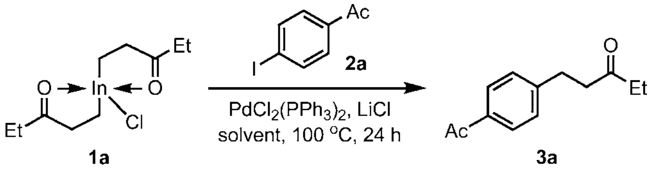
10.1021/ol102755q

indium homoenolate with an aryl halide. However, owing to the low reactivity of the indium homoenolate, our attempt to carry out the palladium-catalyzed coupling of the indium homoenolate with an aryl halide in THF failed. The reaction proceeded sluggishly under the above conditions to furnish the desired product in <5% yield. In order to circumvent the problem, a more comprehensive study was carried out. Herein, we report an efficient palladium-catalyzed cross-coupling of the indium homoenolate with various aryl halides in DMA. The reactions proceeded efficiently at 100 °C to afford the desired products of β-aryl ketones in moderate to good yields with wide functionality compatibility.[14]

Table 1. Screening of Organic Solvents[a]

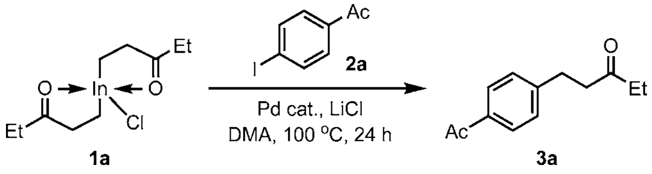


entry	solvent	yield (%)[b]
1	THF[c]	<5
2	1,4-dioxane	<5
3	toluene	<5
4	*n*-PrOH[c]	<5
5	CH_3NO_2	0
6	H_2O	<10
7	NMP	85
8	DMSO	87
9	DMF	78
10	DMA	93

[a] Unless otherwise noted, the reactions were carried out at 100 °C for 24 h using indium homoenolate **1a** (0.3 mmol), aryl iodide **2a** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol), LiCl (1 mmol), and solvent (3 mL). [b] Isolated yield based on aryl iodide **2a** as limiting reagent. [c] Under refluxing conditions.

Initially, various organic solvents were screened in order to optimize the reaction conditions for the palladium-catalyzed coupling of indium homoenolate **1a** with 4-iodoacetophenone (**2a**). As shown in Table 1, the coupling reaction utilizing $PdCl_2(PPh_3)_2$ (5 mol %) as a catalyst

Table 2. Screening of Palladium Catalysts[a]



entry	catalyst	yield (%)[b]
1	$PdCl_2(PPh_3)_2$ (5 mol %)	93
2	$Pd(OAc)_2$ (5 mol %), Me-Phos (10 mol %)	73
3	$Pd(dppf)Cl_2$ (5 mol %)	76
4	$Pd_2(dba)_3$ (2.5 mol %), PPh_3 (10 mol %)	70
5	$Pd(PhCN)_2Cl_2$ (5 mol %), PPh_3 (10 mol %)	76
6	$Pd(PPh_3)_4$ (5 mol %)	81

[a] Unless otherwise noted, the reactions were carried out at 100 °C for 24 h using indium homoenolate **1a** (0.3 mmol), aryl iodide **2a** (0.5 mmol), Pd cat. (0.025 mmol), phosphine ligand (0.05 mmol), LiCl (1 mmol), and DMA (3 mL). [b] Isolated yield based on aryl iodide **2a** as limiting reagent.

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(10) For other selected examples concerning the palladium-catalyzed coupling of R_3In or other types of organoindium reagents with various electrophiles (such as aryl halide, acid chloride, benzyl halides, alkenyl halides), see: (a) Caeiro, J.; Sestelo, J. P.; Sarandeses, L. A. *Chem.—Eur. J.* **2008**, *14*, 741. (b) Pena, M. A.; Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246. (c) Nomura, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738. (d) Lee, P. H.; Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (e) Pena, M. A.; Perez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2003**, 780. (f) Gotov, B.; Kaufmann, J.; Schumann, H.; Schmalz, H. G. *Synlett* **2002**, 361. (g) Jaber, N.; Gelman, D.; Schumann, H.; Dechert, S.; Blum, J. *Eur. J. Org. Chem.* **2002**, 1628. (h) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (i) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901. (j) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993. (k) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (l) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627. (m) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (n) Pena, M. A.; Perez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2005**, 485. (o) Pena, M. A.; Perez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271. (p) Font-Sanchis, E.; Cespedes-Guirao, F. J.; Sastre-Santos, A.; Fernandez-Lazaro, F. *J. Org. Chem.* **2007**, *72*, 3589. (q) Riveiros, R.; Saya, L.; Perez Sestelo, J.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2008**, 1959. (r) Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 9429. (s) Jin, L.; Zhao, Y.; Zhu, L.; Zhang, H.; Lei, A. *Adv. Synth. Catal.* **2009**, *351*, 630.

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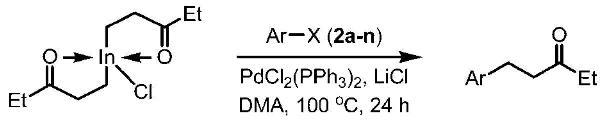
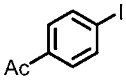
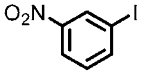
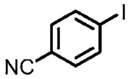
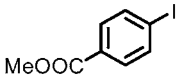
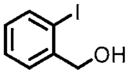
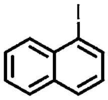
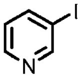
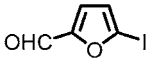
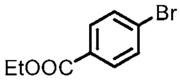
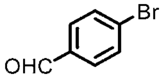
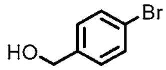
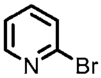
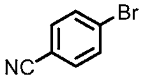
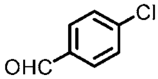
(12) For selected examples associated with the synthesis and application of metal homoenolates in organic synthesis by Kuwajima, Nakamura, Yoshida, Knochel, and others, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (c) Nakamura, E.; Shimada, J.-i.; Kuwajima, I. *Organometallics* **1985**, *4*, 641. (d) Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1985**, *50*, 2802. (e) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745. (f) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 2138. (g) Horiguehi, Y.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1986**, *51*, 4323. (h) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651. (i) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. (j) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559. (k) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418. (l) Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694. (m) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (n) Goswami, R. *J. Org. Chem.* **1985**, *50*, 5907. (o) Cozzi, P. G.; Carofiglio, T.; Floriani, C. *Organometallics* **1993**, *12*, 2845. For the cross-coupling reactions of zinc homoenolates with aryl halides, see: (p) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (q) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.

(13) For reviews regarding the generation of homoenolate intermediates with the use of nucleophilic heterocyclic carbene (NHC) catalysis, see: (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. For recent examples, see: (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (c) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (d) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (e) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (f) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem.* **2006**, *71*, 8964. (g) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (h) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (i) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (j) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098. (k) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (l) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747. (m) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (n) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (o) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (p) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (q) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

Table 3. Substrate Scope Study[a]



1a **3a-l**

entry	substrate		product **3**	yield (%)[b]
1		**2a**	**3a**	93
2		**2b**	**3b**	76
3		**2c**	**3c**	80
4		**2d**	**3d**	76
5		**2e**	**3e**	62
6		**2f**	**3f**	73
7		**2g**	**3g**	64
8		**2h**	**3h**	44
9		**2i**	**3i**	75
10		**2j**	**3j**	66
11		**2k**	**3k**	60
12		**2l**	**3l**	52
13		**2m**	**3c**	76
14		**2n**	**3j**	60

[a] The reactions were carried out at 100 °C for 24 h using indium homoenolate **1a** (0.3 mmol), ArX **2** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol), LiCl (1 mmol), and DMA (3 mL). [b] Isolated yield based on ArX **2** as limiting reagent.

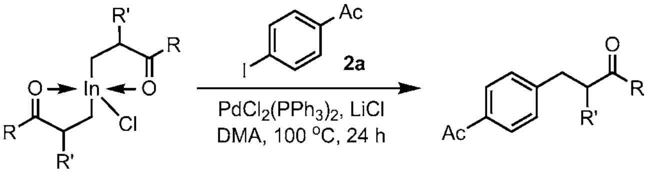
proceeded sluggishly in commonly used organic solvents such as THF, 1,4-dioxane, toluene, *n*-propanol, nitromethane, and water (Table 1, entries 1−6). In sharp contrast, the cross-coupling was dramatically enhanced by employing polar organic solvent such as NMP, DMSO, DMF, and DMA (Table 1, entries 7−10). Optimal results were obtained when DMA was employed as the reaction solvent, affording the desired product **3a** in 93% yield (Table 1, entry 10).

Next, various palladium catalysts were employed to investigate their efficiency in the cross-coupling reactions. As shown in Table 2, all the palladium catalysts screened in the reactions could efficiently catalyze the cross-coupling to furnish the desired product **3a** in good to excellent yields. Among them, the use of $PdCl_2(PPh_3)_2$ (5 mol %) as the catalyst afforded the product **3a** with an excellent yield of 93% (Table 2, entry 1). Thus, the following cross-coupling reactions were chosen to be carried out at 100 °C for 24 h using $PdCl_2(PPh_3)_2$ as the catalyst, LiCl as an additive, and DMA as the solvent.

With the optimized reaction conditions in hand, we continued our task on the exploration of the reaction substrate scope. As shown in Table 3, the cross-coupling of indium homoenolate with various aryl halides proceeded efficiently under optimized conditions to furnish the β-aryl ketones in moderate to good yields. A range of important functional groups which were sensitive to organomagnesium and/or organozinc reagents can be well tolerated in the cross-coupling reactions. For instance, functional groups including COR, NO_2, CN, COOR, and CHO were compatible to the reaction conditions. Especially noteworthy, the reactions using substrates **2e** and **2k** bearing a free hydroxyl group occurred smoothly without any protection, generating the cross-coupling products **3e** and **3k** in acceptable yields of 62 and 60%, respectively (Table 3, entries 5 and 11). In addition, heterocyclic halides such as **2g**, **2h**, and **2l** can be employed in the reactions as well (Table 3, entries 7, 8, and 12). Furthermore, less reactive aryl chloride **2n** was also proven as a good candidate for the coupling reaction leading to the expected product **3j** in 60% yield (Table 3, entry 14).

Next, we turned our attention to the cross-coupling of aryl iodide **2a** with a range of indium homoenolates. As shown in Table 4, both aliphatic substituted indium homoenolates (entries 1 and 2) and aromatic substituted indium homoeno-

Table 4. Substrate Scope Study[a]



1a-f **3a, m-q**

entry	R	R'	product **3**	yield (%)[b]
1	Et	H	**3a**	93
2	*n*-pentyl	H	**3m**	77
3	Ph	H	**3n**	82
4	4-ClC_6H_4	H	**3o**	85
5	2-thienyl	H	**3p**	70
6	Ph	Me	**3q**	69

[a] The reactions were carried out at 100 °C for 24 h using indium homoenolate **1** (0.3 mmol), ArI **2a** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol), LiCl (1 mmol), and DMA (3 mL). [b] Isolated yield based on ArI **2a** as limiting reagent.

lates (entries 3−5) worked well in our protocol, leading to good isolated yields of the corresponding products. Additionally, an indium homoenolate possessing a methyl group at α-position to the carbonyl group also can be effectively converted to give the desired product **3q** in 69% yield (Table 4, entry 6).

In summary, an efficient palladium-catalyzed cross-coupling of indium homoenolates with various aryl halides in DMA was described. The reactions proceeded efficiently to afford the desired products of β-aryl ketones in moderate to good yields. Various functional groups including COR, COOR, CHO, CN, OH, and NO_2 can be well tolerated in the protocol which renders the method synthetically useful in organic synthesis. Further studies pertaining to the synthetic utility of the indium homoenolate in organic synthesis are currently underway.

Acknowledgment. We gratefully acknowledge Nanyang Technological University (NTU), Ministry of Education (No. M45110000), and an A*STAR SERC grant (No. 0721010024) for the funding of this research.

Supporting Information Available: Experimental procedures, characterization data of products, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102755Q

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(14) For selected recent examples associated with the development of transition-metal-catalyzed cross-coupling reactions with wide functional group compatibility, see: (a) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920. (b) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592.