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Cobalt-Catalyzed Cross-Coupling of α-Bromo Amides with Grignard Reagents

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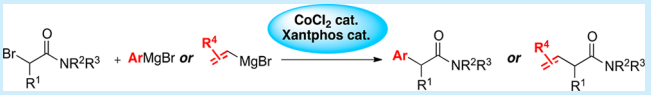
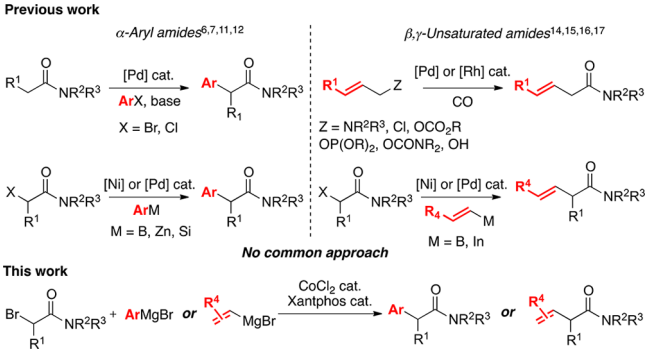
Supporting Information

ABSTRACT: A cobalt-catalyzed cross-coupling between α-bromo amides and Grignard reagents is disclosed. The reaction is general and allows access to a large variety of α-aryl and β,γ-unsaturated amides. Some mechanistic investigations have been undertaken to determine the nature of the intermediate species.



Amides are ubiquitous in both chemical and biological entities. They are present in numerous natural products, pharmaceuticals, synthetic polymers, and functional materials, and they constitute the backbone of all natural peptides.[1] As such, the formation or the functionalization of amides remains a significant research area in organic chemistry. Particularly, α-aryl amides are important pharmacophores present in various biologically active compounds such as atenolol,[2] which is used in the treatment of cardiovascular diseases, or almorexant,[3] which helps to overcome insomnia. In addition, α-aryl amides are precursors of β-aryl amines[4] and of α-aryl carboxylic acids, these latter being a key motif in several nonsteroidal anti-inflammatory drugs.[5] Currently, the most widespread method to access α-aryl amides is the metal-catalyzed arylation of amide enolates.[6,7] However, these reactions generally require the use of strong bases to generate the enolate, thus reducing the functional group tolerance.[8,9] An alternative strategy avoiding the detrimental deprotonation step is a metal-catalyzed cross-coupling between α-halo amides and organometallics. Palladium-catalyzed Suzuki cross-couplings were first developed on α-bromo amides lacking β-hydrogen.[10] Suzuki, Hiyama, and Negishi cross-couplings were then performed on substituted α-halo amides using nickel complexes, which are less prone to β-H elimination.[11,12] β,γ-Unsaturated amides are also useful synthetic intermediates that can be notably transformed into homoallyl amines.[13] They are generally accessed through carbonylation using carbon monoxide,[14,15] and few examples of metal-catalyzed alkenylation of α-halo amides have been reported to date (Scheme 1).[16,17] All the reported arylations or alkenylations of α-halo amides require cost-effective and/or toxic Ni- and Pd-catalysts. In addition, to the best of our knowledge, there is no general method for the synthesis of either α-aryl or α-alkenyl amides from common α-halo amide precursors. In the course of our ongoing studies on metal-catalyzed cross-couplings,[18] we decided to investigate the arylation and alkenylation of α-bromo amides focusing on earth-abundant and cheap first row metal catalysts. Herein, we report a cobalt-catalyzed cross-coupling between α-bromo amides and Grignard reagents.[19] This simple and general method allows access to both α-aryl and β,γ-unsaturated amides using similar conditions and precursors.

Scheme 1. Access to α-Aryl and β,γ-Unsaturated Amides



The arylation of *N*,*N*-dibenzyl-2-bromopentanamide **1a** using phenylmagnesium bromide was examined to determine the appropriate catalytic system. In the absence of any metal catalyst or ligand, the coupling product **2a** was formed but the dehalogenated amide **3a** was obtained as the major product (**2a**/**3a** = 23:77) (Table 1, entry 1). The dehalogenation may proceed through a bromine−magnesium exchange leading to a magnesium enolate. To prevent this undesired process, metal catalysts were introduced in the reaction mixture. Based on our previous results in Fe- and Co-catalyzed cross-couplings,[18c,d] (*R*,*R*)-tetramethylcyclohexan-1,2-diamine (TMCD) was selected as a ligand and a panel of metal complexes were screened. Unfortunately, the use of iron salts led to either incomplete conversion of **1a** or formation of the dehalogenated product **3a** as the major product.[20] Using the nonhygroscopic $Co(acac)_3$, the arylation failed as, once again, the amide **3a** was the major compound (Table 1, entry 2). To our delight, when the simple and cost-effective $CoCl_2$ was utilized, the arylated compound **2a** was the main product which was isolated with an encouraging yield of 58% (Table 1, entry 3). Thus, $CoCl_2$ was selected and a range of ligands were examined. Replacing TMCD by tetramethylethylenediamine (TMEDA) increased the formation

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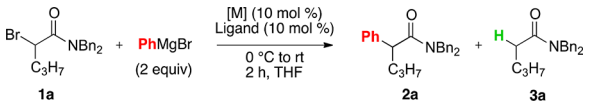
of the dehalogenated compound (Table 1, entry 4). Several diphosphine ligands were then associated with $CoCl_2$, and among them, Xantphos was the most promising.[20,21] Using an equimolar mixture of $CoCl_2$ and Xantphos (10 mol % each) allowed the isolation of **2a** with a good yield of 70% (Table 1, entry 5). Noteworthy, the reaction could be performed on a gram scale without affecting the yield.[22,23]

Table 1. Optimization of the Reaction Conditions

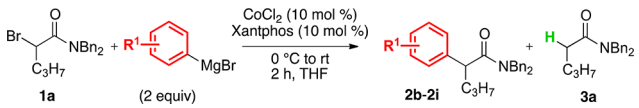


entry	[M]	ligand	conversion of **1a**[a]	**2a**/**3a**[b]	**2a** (yield%)[c]
1	–	–	100%	23:77	nd
2	$Co(acac)_3$	TMCD[d]	100%	10:90	nd
3	$CoCl_2$	TMCD[d]	100%	85:15	58%
4	$CoCl_2$	TMEDA[d]	100%	58:42	nd
5	$CoCl_2$	Xantphos[d]	100%	92:8	70%

[a]Transformation of **1a** into **2a** and **3a** estimated on the crude ^{1}H NMR. [b]Determined on the crude ^{1}H NMR spectrum. [c]Isolated yield. [d]TMCD: (*R*,*R*)-tetramethylcyclohexan-1,2-diamine; TMEDA: tetramethylethylenediamine; Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

With these optimized conditions in hand, the scope of the arylation was evaluated by varying the aryl Grignard reagent. Electron-rich *p*-tolylphenylmagnesium bromide and *p*-methoxyphenylmagnesium bromide were efficiently coupled to bromo amide **1a** delivering the expected products in ca. 68% yield (Table 2, entries 1−2). Similarly, when **1a** was reacted with the *p*-dimethylaminophenylmagnesium bromide, the coupling product was isolated with a satisfying yield of 64%. Surprisingly, in this latter case, when the Grignard reagent was prepared according to Knochel's procedure (Mg, LiCl, DIBAL-H cat.),[24] the yield in the coupling product dropped to 48% (Table 2, entry 3). The presence of LiCl seems to interfere with the reaction outcome, favoring side reactions.[25] Electron-poor Grignard reagents such as *p*-trifluoromethylmagnesium bromide and *p*-fluorophenylmagnesium bromide were reactive under the coupling conditions, furnishing **2e** and **2f** in 70% and 58% yields respectively (Table 2, entries 4−5). Using *p*-chlorophenylmagnesium bromide led to the formation of the corresponding coupling product **2g** with a good yield of 73% (Table 2, entry 6). Interestingly, the presence of a chlorine atom offers subsequent functionalization opportunities. A *meta*-substituent on the phenyl ring of the Grignard was well tolerated (Table 2, entry 7). In contrast, the reaction was sensitive to steric hindrance, as by using *o*-tolylmagnesium bromide, the dehalogenated amide **3a** was the major product formed under the developed conditions (Table 2, entry 8).

Table 2. Variation of the Aryl Grignard Reagent

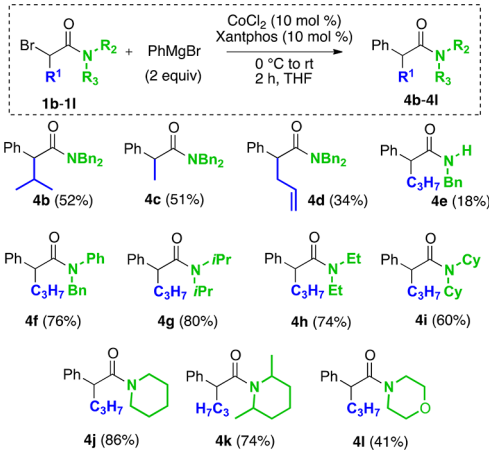


entry	R^1	**2** (yield%)[a,26]
1	*p*-Me[b]	**2b** (68%)
2	*p*-OMe[b]	**2c** (69%)
3	*p*-NMe_2	**2d** (64%,[c] 48%[d])
4	*p*-CF_3	**2e** (70%,[c] 41%[d])
5	*p*-F[b]	**2f** (58%)
6	*p*-Cl[b]	**2g** (73%)
7	*m*-OMe[b]	**2h** (70%)
8	*o*-Me[b]	**2i** (0%)

[a]Isolated yield. [b]Commercially available Grignard reagents were used. [c]The Grignard reagent was prepared using classical method (Mg, THF). [d]The Grignard reagent was prepared according to Knochel et al. procedure (Mg, LiCl, THF).[24]

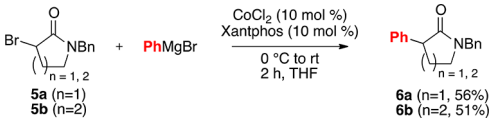
A panel of amide partners **1b−1d** bearing various side chains (R^1) were then reacted with phenylmagnesium bromide in the presence of the catalytic system. The corresponding coupling products **4b−4d** were isolated in moderate yields ranging from 34% to 52%. The reaction was inefficient on secondary amides such as **4e**, but a variety of tertiary amides were well tolerated under the optimized conditions. One of the *N*-benzyl substituents could be replaced by a phenyl group without affecting the yield (**4f**, 76%). Different alkyl substituents ($R^2 = R^3$ = *i*Pr, Et, Cy) could be introduced on the nitrogen atom, and the coupling products **4g−4i** were isolated with yields up to 80%. The nitrogen atom could be part of a heterocycle, and high yields were obtained for the synthesis of piperidine-containing products **4j** and **4k**. The α-phenyl amide **4l** possessing a morpholine moiety was obtained with a lower yield of 41% (Scheme 2).

Scheme 2. Variation of the Amide Partner



Pleasingly, the arylation of α-bromo lactams such as **5a** and **5b** was successful and the corresponding coupling products were isolated with moderate yields of 56% and 51% (Scheme 3).

Scheme 3. Coupling Involving Bromo Lactams



Following these encouraging results, the alkenylation of α-bromo amides was next examined. Decreasing the temperature to −40 °C was necessary to obtain good yields in coupling products. Reaction between **1a** and vinylmagnesium bromide afforded **7a** in 63% yield. Alkenyl Grignard reagents possessing various substitution patterns on the double bond were involved in the process, resulting in the formation of coupling products

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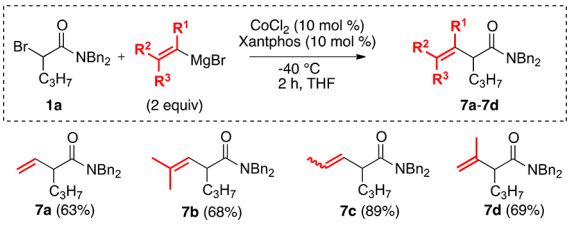
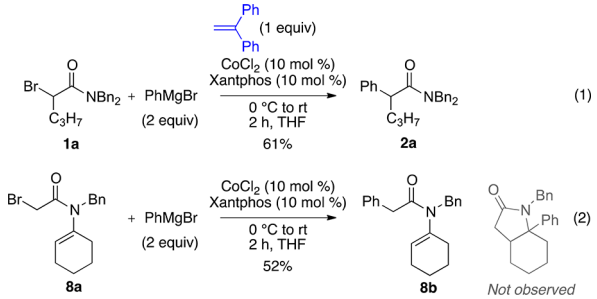
7b–**7d** in good yields up to 89%. Thus, the developed cross-coupling appears as a valuable method for the synthesis of β,γ-unsaturated amides (Scheme 4).

Scheme 4. Alkenylation of α-Bromo Amide 1a



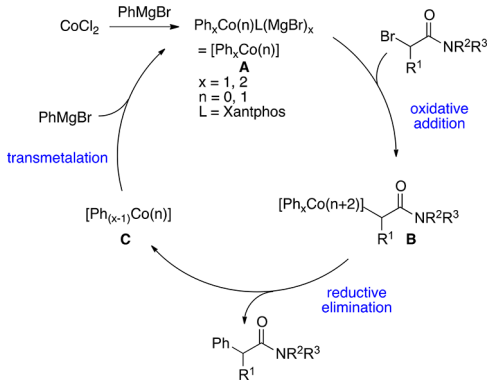
To gain some mechanistic insight, two elementary experiments were carried out. The formation of radical intermediates during cobalt-catalyzed cross-couplings between alkyl halides and aryl Grignard reagents has already been demonstrated.[18,27] These radicals would be formed through two successive single-electron transfers composing the formal oxidative addition. A first experiment was conducted in the presence of a radical scavenger. When **1a** was treated with phenylmagnesium bromide in the presence of 1 equiv of 1,1-diphenylethylene under the optimized conditions, the coupling product was obtained with a slightly decreased yield of 61% (versus 70%) and no trace of an adduct resulting from the addition on 1,1-diphenylethylene was observed (Scheme 5, eq 1). In addition, the bromo amide **8a** was used as a radical clock. Under classical radical conditions (Bu_3SnH, AIBN), this compound has been shown to deliver the corresponding lactam through a 5-*endo-trig* cyclization.[28] However, in our case, the cobalt-catalyzed cross-coupling conditions applied to **8a** only afforded the linear coupling product and no trace of a cyclized compound could be detected (Scheme 5, eq 2). These two results suggest that α-bromo amides exhibit different behavior from nonactivated alkyl halides and a concerted oxidative addition may be hypothesized excluding the formation of radicals. However, kinetic considerations cannot be ignored and the absence of cyclic product starting from **8a** could also be explained by a coupling that could be faster than the cyclization process.

Scheme 5. Mechanistic Studies



Based on our observations and on literature reports,[27] a hypothetical mechanism is depicted on Scheme 6. The first step may consist of a reduction of $CoCl_2$ by the Grignard reagent into the active species. However, the oxidation state of the cobalt remains unclear and Co(0)[27e] as well as Co(I)[29] could be proposed. A concerted oxidative addition may deliver intermediate **B**, which may lead to the desired product together with complex **C** after reductive addition. A transmetalation of **C** with the Grignard reagent may regenerate catalyst **A**. The Xantphos ligand may accelerate the reductive elimination step, thus increasing the turnover and inhibiting the noncatalyzed dehalogenation process.[30]

Scheme 6. Hypothetic Mechanism



In summary, a cobalt-catalyzed cross-coupling between α-bromo amides and Grignard reagents has been developed giving access to both α-aryl and β,γ-unsaturated amides. To the best of our knowledge, it is the first unified approach toward the formation of these two important motifs. The reaction is general and scalable and involves a cost-effective cobalt catalyst and easily available Grignard reagents. Therefore, it can be considered as a potent attractive synthetic tool for the functionalization of amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02848.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected book and reviews: (a) Greenberg, A.; Breneman, L. M.; Liebman, J. F. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry and Materials Science*; Wiley: New York, 2000. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (c) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405. (d) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (e) Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. *Chem. Rev.* **2012**, *112*, 5271. (f) de Figueiredo, R. M.; Suppo,

DOI: 10.1021/acs.orglett.7b02848
Org. Lett. XXXX, XXX, XXX–XXX

J.-S.; Campagne, J.-M. *Chem. Rev.* **2016**, *116*, 12029 and references therein.
(2) (a) Carlberg, B.; Samuelsson, O.; Lindholm, L. H. *Lancet* **2004**, *364*, 1684. (b) Agon, P.; Goethals, P.; Haver, D. V.; Kaufman, J. *J. Pharm. Pharmacol.* **1991**, *43*, 597. (c) Akisanya, J.; Parkins, A. W.; Steed, J. W. *Org. Process Res. Dev.* **1998**, *2*, 274. (d) Bose, S.; Narsaiah, A. V. *Bioorg. Med. Chem.* **2005**, *13*, 627. (e) Dwivedee, B. P.; Ghosh, S.; Bhaumik, J.; Banoth, L.; Banerjee, U. C. *RSC Adv.* **2015**, *5*, 15850.
(3) (a) Owen, R. T.; Castañer, R.; Bolós, J.; Estivill, C. *Drugs Future* **2009**, *34*, 5. (b) Fañanás-Mastral, M.; Teichert, J. F.; Fernández-Salas, J. A.; Heijnen, D.; Feringa, B. L. *Org. Biomol. Chem.* **2013**, *11*, 4521. (c) Reddy, N. S. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2014**, *55*, 3157.
(4) See for example: (a) Jullian, V. *Synthesis* **1997**, *1997*, 1091. (b) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. (c) Wang, M.-X.; Zhao, S.-M. *Tetrahedron Lett.* **2002**, *43*, 6617.
(5) Hart, F. D.; Huskisson, E. C. *Drugs* **1984**, *27*, 232.
(6) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (e) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190. (f) Zheng, B.; Jia, T.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 165 and references therein.
(7) For other methods of amides α-arylation, see for example: (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Lai, P.-S.; Dubland, J. A.; Sarwar, M. G.; Chudzinski, M. G.; Taylor, M. S. *Tetrahedron* **2011**, *67*, 7586. (c) Romero, O.; Castro, A.; Terán, J. L.; Gnecco, D.; Orea, M. L.; Mendoza, A.; Flores, M.; Roa, L. F.; Juárez, J. R. *Tetrahedron Lett.* **2011**, *52*, 5947. (d) Zhao, L.; Baslé, O.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 4106. (e) Liu, C.; Liu, D.; Zhang, W.; Zhou, L.; Lei, A. *Org. Lett.* **2013**, *15*, 6166. (f) Li, Y.; Hu, B.; Dong, W.; Xie, X.; Wan, J.; Zhang, Z. *J. Org. Chem.* **2016**, *81*, 7036. (g) Moon, P. J.; Halperin, H. M.; lundgren, R. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 1894.
(8) The requirement for strong bases is due to high pK_a values of amide α-CH bond; see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(9) To circumvent this difficulty, the arylation of zinc amide enolates has been developed; see for example: (a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (b) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (c) Cossy, J.; de Filippis, A.; Gomez-Pardo, D. *Org. Lett.* **2003**, *5*, 3037. (d) Cossy, J.; de Filippis, A.; Gomez-Pardo, D. *Synlett* **2003**, 2171. (e) de Filippis, A.; Gomez-Pardo, D.; Cossy, J. *Synthesis* **2004**, *2004*, 2930. (f) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105. (g) Michon, C.; Béthegnies, A.; Capet, F.; Roussel, P.; de Filippis, A.; Gomez-Pardo, D.; Cossy, J.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2013**, *2013*, 4979.
(10) (a) Gooβen, L. J. *Chem. Commun.* **2001**, 669. (b) Duan, Y.-Z.; Deng, M.-Z. *Tetrahedron Lett.* **2003**, *44*, 3423.
(11) (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594. (b) Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, *9*, 5601. (c) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. (d) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027. (e) Tarui, A.; Shinohara, S.; Sato, K.; Omote, M.; Ando, A. *Org. Lett.* **2016**, *18*, 1128.
(12) One example of iron-catalyzed arylation of amide lacking β-hydrogen atom has been reported: Jin, M.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1012.
(13) Selected examples: (a) Wilson, S. R.; Di Grandi, M. J. *J. Org. Chem.* **1991**, *56*, 4766. (b) Brummond, K. M.; Hong, S.-P. *J. Org. Chem.* **2005**, *70*, 907. (c) Díaz, D. D.; Ramírez, M. A.; Martín, V. S. *Chem. - Eur. J.* **2006**, *12*, 2593. (d) Combettes, L. E.; Schuler, M.; Patel, R.; Bonillo, B.; Odell, B.; Thompson, A. L.; Claridge, T. D. W.; Gouverneur, V. *Chem. - Eur. J.* **2012**, *18*, 13126. (e) Nidhiry, J. E.; Prasad, N. R. *Synlett* **2014**, *25*, 2585.
(14) Selected examples: (a) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1578. (b) Murahashi, S.-I.; Imada, Y.; nishimura, K. *Tetrahedron* **1994**, *50*, 453. (c) Mitsudo, T.-A.; Suzuki, N.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 7759. (d) Yu, H.; Zhang, G.; Liu, Z.-J.; Huang, H. *RSC Adv.* **2014**, *4*, 64235. (e) Fang, X.; Li, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 16039. (f) Li, H.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2016**, *22*, 10050. (g) Li, H.; Fang, X.; Jackstell, R.; Neumann, H.; Beller, M. *Chem. Commun.* **2016**, *52*, 7142 and referenes therein.
(15) For another recent method avoiding the use of CO, see: Qiu, G.; Mamboury, M.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 15377.
(16) (a) Deng, M.-Z.; Li, N.-S.; Huang, Y.-Z. *J. Chem. Soc., Chem. Commun.* **1993**, 65. (b) Luo, F.-T.; Lu, T.-Y.; Xue, C. *Tetrahedron Lett.* **2003**, *44*, 7249. (c) Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751. (d) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4555. (e) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. (f) Molander, G. A.; Barcellos, T.; Traister, K. M. *Org. Lett.* **2013**, *15*, 3342.
(17) For the alkenylation of halo amides via radical reactions, see: (a) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229. (b) García-Torres, A.; Cruz-Almanza, R.; Miranda, L. D. *Tetrahedron Lett.* **2004**, *45*, 2085. (c) Xu, T.; Hu, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1307. (d) Li, Z.; García-Domínguez, A.; Nevado, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 6938. (e) Lu, X.-Y.; Liu, J.-H.; Lu, X.; Zhang, Z.-Q.; Gong, T.-J.; Xiao, B.; Fu, Y. *Chem. Commun.* **2016**, *52*, 5324.
(18) (a) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521. (b) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101. (c) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett.* **2014**, *16*, 6160. (d) Gonnard, L.; Guérinot, A.; Cossy, J. *Chem. - Eur. J.* **2015**, *21*, 12797.
(19) For reviews on Co-catalyzed cross-couplings, see: (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (b) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221.
(20) See the Supporting Information for the whole optimization study.
(21) Concerning the use of Xantphos in catalysis, see: Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895.
(22) When the corresponding chloro amide **1a′** was used, a lower yield of 45% was obtained.
(23) The catalytic loading can be reduced to 5 mol % for both $CoCl_2$ and Xantphos delivering **2a** in 62% yield.
(24) Piller, F.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.
(25) The detrimental influence of LiCl was confirmed by adding 1 equiv of LiCl to PhMgBr for the coupling of **1a**. The reaction was sluggish, and the coupling product was isolated with a low 29% yield.
(26) The moderate yields obtained are generally due to the formation of the dehalogenated product causing troublesome purifications.
(27) (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (b) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. - Eur. J.* **2004**, *10*, 5640. (c) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068. (d) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886. (e) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (f) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565. (g) Someya, H.; Ohmiya, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 8609.
(28) See for example: (a) Ishibashi, H.; Matsukida, H.; Toyao, A.; Tamura, O.; Takeda, Y. *Synlett* **2000**, 1497. (b) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537. (c) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437.
(29) See for example: (a) Klein, L. J.; Alleman, K. S.; Peters, D. G.; Karty, J. A.; Reilly, J. P. *J. Electroanal. Chem.* **2000**, *481*, 24. (b) Buriez, O.; Nédélec, J.-Y.; Périchon, J. *J. Electroanal. Chem.* **2001**, *506*, 162. (c) Buriez, O.; Cannes, C.; Nédélec, J.-Y.; Périchon, J. *J. Electroanal. Chem.* **2000**, *495*, 57.
(30) Shi, W.; Liu, C.; Yu, Z.; Lei, A. *Chem. Commun.* **2007**, 2342.

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