OL | Organic Letters

pubs.acs.org/OrgLett Letter

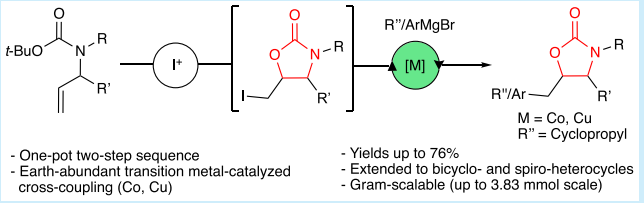
A One-Pot Iodo-Cyclization/Transition Metal-Catalyzed Cross-Coupling Sequence: Synthesis of Substituted Oxazolidin-2-ones from *N*-Boc-allylamines

Pauline Chaumont-Olive and Janine Cossy*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01114 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A one-pot iodo-cyclization/transition metal-catalyzed cross-coupling sequence is reported to access various C5-functionalized oxazolidin-2-ones from unsaturated *N*-Boc-allylamines. Depending on the Grignard reagents used for the cross-coupling, e.g., aryl- or cyclopropylmagnesium bromide, a cobalt or copper catalyst has to be used to obtain the functionalized oxazolidin-2-ones in good yields.



Oxazolidin-2-ones have been widely developed especially as chiral auxiliaries since the development of Evans aldolization using C4-functionalized oxazolidin-2-ones.[1] Despite the fact that C5-functionalized oxazolidin-2-ones have low benefit toward chiral induction, they are of interest as biologically active compounds. In 1978, E.I. Du Pont de Nemours and Company reported for the first time their antibiotic activity,[2] and since then, these heterocycles are highly represented among several bioactive compounds, such as linezolid and derivatives as antibacterial agents,[3] the antidepressant toloxatone,[4] and fenspiride, a bronchodilator.[5] In addition, functionalized oxazolidin-2-ones are also present in alkaloid natural products such as in the stemoxazolidinone family[6] (Figure 1).

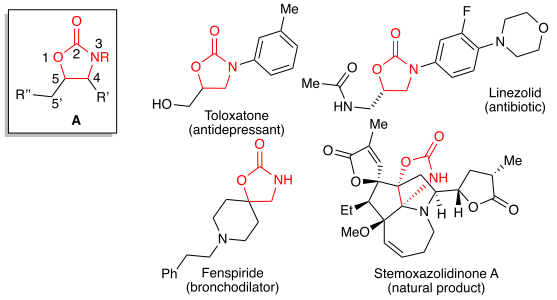
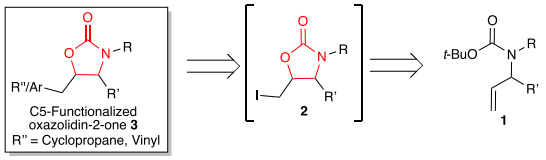


Figure 1. C5-functionalized oxazolidin-2-ones in drugs and natural products.

Despite a large range of synthetic methods leading to such heterocycles,[7] CO_2 insertion into amino alcohols, epoxy amines, or aziridines was developed.[8] However, an efficient strategy allowing the synthesis of oxazolidin-2-ones of type **A** by introducing a diversity of R′′/Ar groups at the C5′ position, at a late stage, would be of interest (Figure 1).

Nowadays, the development of methods in organic synthesis is mainly driven by the use of nontoxic, cheap, and earth-abundant metals. For example, in cross-couplings, the replacement of palladium catalysts by metals of the fourth row of the periodic table, such as Fe, Co, Ni, and Cu, is favored.[9−13] In the context of our studies on cobalt-catalyzed cross-couplings between alkyl halides and Grignard reagents,[14] we report herein a one-pot iodo-cyclization/cross-coupling sequence to access a diversity of C5-functionalized oxazolidin-2-ones **3** from easily accessible unsaturated *N*-Boc-allylamines (Scheme 1).

Scheme 1. Synthesis of C5-Functionnalized Oxazolidin-2-ones 3 from *N*-Boc-allylamines 1

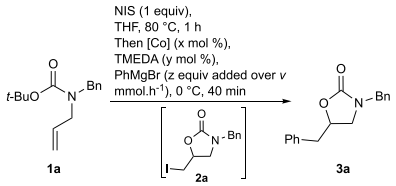


At first, the intramolecular iodo-cyclization starting from *N*-Boc-*N*-benzyl-allylamine **1a** (R = Bn, R′ = H) was optimized (see Table S1). The best reaction conditions to access *N*-benzyl-5-iodomethyloxazolidin-2-one **2a** were found to be the use of *N*-iodosuccinimide (NIS) (1 equiv) in refluxing THF (c = 0.67 mol·L^{-1}), in a sealed tube for 1 h,

Received: March 27, 2020

leading to **2a** which was isolated in 80% yield. Having the best conditions to access the iodo derivatives **2**, the one-pot iodocyclization/cross-coupling was then examined, and the optimization of the reaction conditions was achieved (Table 1). Based on our previous experience,[14] once the iodocyclization to access intermediate **2a** was complete, the cross-coupling of this latter with PhMgBr (1.5 equiv, rate of addition v = 0.26 mmol·h^{-1}) was explored by screening various cobalt salts (at 0 °C for 40 min). By using $CoCl_2$ (15 mol %) in the presence of a diamine ligand such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 1 equiv), only traces of the expected compound **3a** were observed, while $Co(acac)_2$ (15 mol %) gave **3a** in 9% yield (^{1}H NMR yield) and $Co(acac)_3$ (15 mol %) led to **3a** in 11% yield (^{1}H NMR yield) (Table 1, entries 1−3). Using $Co(acac)_3$ and increasing the excess of PhMgBr from 1.5 to 3 equiv, **3a** was formed in 47% yield (^{1}H NMR yield) (Table 1, entry 4). Pleasingly, when the addition rate of PhMgBr was increased from 0.26 to 0.52 mmol·h^{-1}, **3a** was isolated in 74% yield (Table 1, entry 5). In addition, upon decreasing the catalyst loading of $Co(acac)_3$, from 15 to 10 mol %, and the amount of TMEDA, from 100 to 40 mol %, with a faster addition rate of PhMgBr (1.04 versus 0.52 mmol·h^{-1}), **3a** could be isolated with a good yield of 76% (Table 1, entry 6). It is worth mentioning that the use of copper salts [CuI and $CuCl_2$ (15 mol %)] did not allow the cross-coupling of the iodo-oxazolidin-2-one intermediate **2a** (formed *in situ*) with PhMgBr as **3a** was not observed (see Table S2). Furthermore, iron salts [$FeCl_2$, $FeCl_3$ and $Fe(acac)_3$ (15 mol %) in the presence of TMEDA (1 equiv)] allowed the formation of the oxazolidin-2-one **3a**, but in low yield (see Table S2).

Table 1. Optimization of the Reaction Conditions for the Cross-Coupling in a One-Pot Sequence to Access Oxazolidin-2-one 3a from *N*-Boc-*N*-benzylallylamine 1a Using PhMgBr

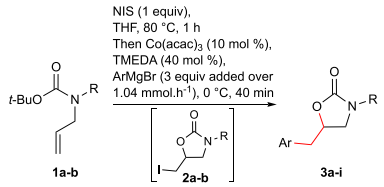


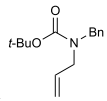
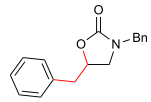
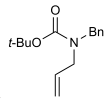
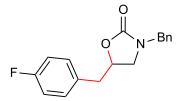
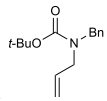
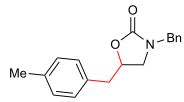
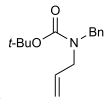
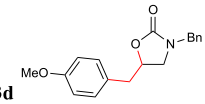
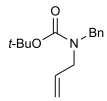
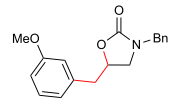
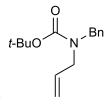
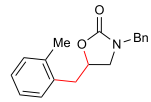
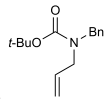
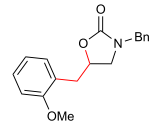
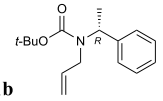
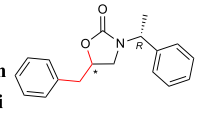
entry	[Co] (x mol %)	TMEDA (y mol %)	PhMgBr (z equiv)	v (mmol·h^{-1})	**3a** (%)[a]
1	$CoCl_2$ (15)	100	1.5	0.26	traces
2	$Co(acac)_2$ (15)	100	1.5	0.26	9
3	$Co(acac)_3$ (15)	100	1.5	0.26	11
4	$Co(acac)_3$ (15)	100	3	0.26	47
5	$Co(acac)_3$ (15)	100	3	0.52	74[b]
6	$Co(acac)_3$ (10)	40	3	1.04	76[b]

[a]^{1}H NMR yield determined by using 1,3-dimethoxybenzene as internal standard. [b]Isolated yield.

With the optimized reaction conditions in hand, the scope of the one-pot, two-step process was examined with various aryl Grignard reagents and *N*-Boc-allylamines **1**, allowing the access to C5-functionalized oxazolidin-2-ones (**3a**−**i**) (Table 2), bicyclic oxazolidin-2-ones (**3j**−**l**) and a spirocyclic derivative (**3m**) (Table 3). When electron-poor substituents are present in the *para* position of the aryl Grignard reagent, such as a fluorine atom or, when electron-rich substituents are present in

Table 2. Scope of the One-Pot Two-Step Sequence to Access C5-Functionalized Oxazolidin-2-ones 3a−i from *N*-Boc-allylamines 1a and 1b Using Various Arylmagnesium Bromide



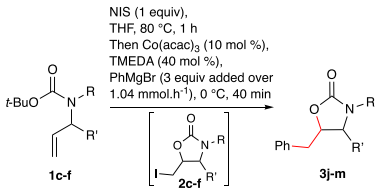
entry	starting material, **1**	product, **3**	yield (%)
1	 **1a**	 **3a**	76
2	 **1a**	 **3b**	65
3	 **1a**	 **3c**	68
4	 **1a**	 **3d**	62
5	 **1a**	 **3e**	60
6	 **1a**	 **3f**	34
7	 **1a**	 **3g**	37
8	 **1b**	 (*R*,*S*)-**3h** (*R*,*R*)-**3i**	31[a, b] 31[a, b]

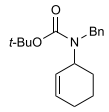
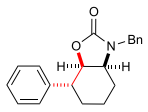
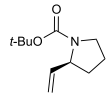
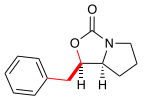
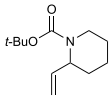
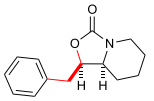
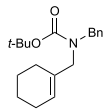
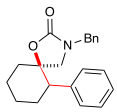
[a]**3h** and **3i** were obtained with 98% purity. [b]Over 3.83 mmol scale (1 g), **3h** was isolated with a yield of 33% and **3i** with a yield of 22%.

the *para* position of the aryl group such as a methyl or a methoxy substituent, the corresponding cyclized/coupled products **3b**, **3c**, and **3d** were isolated in good yields (65%, 68%, and 62% yield, respectively) (Table 2, entries 2−4). The *m*-methoxyphenyl Grignard reagent gave also the expected oxazolidin-2-one **3e** in 60% yield (Table 2, entry 5). Sterically hindered *ortho*-substituted Grignard reagents such as the *o*-methylphenyl- or the *o*-methoxyphenylmagnesium bromide led to the corresponding oxazolidin-2-ones **3f** and **3g** in 34% and 37% moderate yields, respectively (Table 2, entries 6 and 7). To access enantioenriched oxazolidin-2-ones, *N*-Boc,*N*-[(*R*)-phenylethyl]allylamine **1b** was treated with PhMgBr, and under the optimized reaction conditions, the two diastereomeric oxazolidin-2-ones **3h** and **3i** were obtained in a 1:1 ratio

https://dx.doi.org/10.1021/acs.orglett.0c01114
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Scope of the One-Pot Two-Step Sequence to Access Bicyclo- and Spiro-oxazolidin-2-ones 3j−m from *N*-Boc-allylamines 1c−f Using PhMgBr



entry	starting material, **1**	product, **3**	yield (%) (dr)
1	 **1c**	 **3j**	64 (96:04)
2	 **1d**	 **3k**	51 (90:10)
3	 **1e**	 **3l**	61 (65:35)
4	 **1f**	 **3m**[a]	11 (95:05)

[a]Relative stereochemistry not determined.

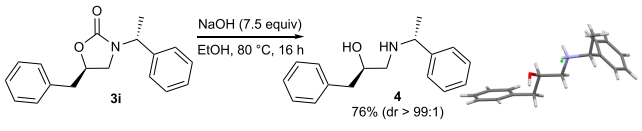
(determined by ^{1}H NMR analysis of the crude reaction mixture). These two diastereomers were easily separated by silica gel column chromatography, and each of them was isolated in 31% yield (Table 2, entry 8). This sequence of reactions was scaled up (from 0.22 to 3.83 mmol with an increase of the addition rate of PhMgBr from 1.04 to 11.47 mmol·h^{-1}), affording **3h** and **3i** in a 60:40 ratio (determined by ^{1}H NMR analysis of the crude reaction mixture) and isolated in 33% and 22% yields, respectively, after purification by silica gel column chromatography.[15]

As the oxazolidin-2-ones offer the opportunity to access amino alcohols, **3i** was treated with NaOH (in refluxing EtOH, 16 h) to afford **4** in 76% yield (Scheme 2). Compound **4** was transformed to its crystalline ammonium chloride salt, and the absolute configuration of the carbon substituted by the hydroxyl was determined by X-ray diffraction analysis. This analysis confirmed at the same time the absolute configuration of the C5 stereogenic center of the oxazolidin-2-one **3i**. It is worth noting that the amino alcohol **4** can be utilized to synthesize various heterocycles.[16]

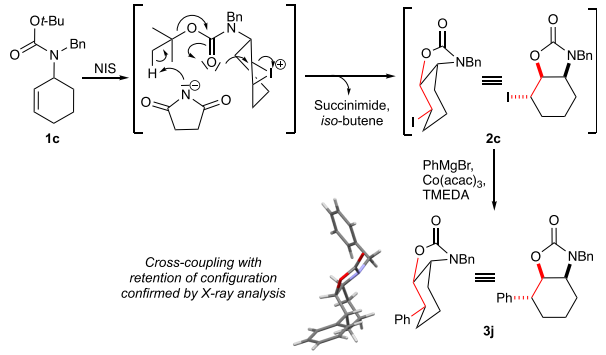
Bicyclo- and spiro-heterocycles containing an oxazolidin-2-one core appear to be interesting compounds as they can be precursors of azasugars[17] as well as natural products[6,18] and/or bioactive compounds.[5,18,19] Thus, by reacting *N*-Boc,*N*-benzyl-cylohex-2-ene-1-amine **1c**, (*S*)-*N*-Boc-2-vinylpyrrolidine **1d**, and *N*-Boc-2-vinylpiperidine **1e** with PhMgBr under the optimized reaction conditions, the corresponding bicyclic compounds **3j**, **3k**, and **3l** were isolated in 64% yield (dr = 96:4), 51% yield (dr = 90:10), and 61% yield (dr = 65:35), respectively (Table 3, entries 1−3). In addition, the unsaturated *N*-Boc substrate **1f** afforded the spirocyclic compound **3m**, albeit in low yield (11%) but with a good dr of 95:5 (Table 3, entry 4).

The relative configuration of the stereogenic centers of the bicyclic oxazolidin-2-one **3j** was confirmed by X-ray diffraction analysis. To explain the formation of **3j**, we can envisage that, after the formation of the iodonium ion intermediate, an *anti* attack of the *tert*-butyl carbamate group on the iodonium implies than the C−O and C−I bonds are in a *trans* relationship, leading to the iodine intermediate **2c**. Thereafter, the cross-coupling of **2c** with PhMgBr, catalyzed by Co(acac)$_3$/TMEDA, was achieved and a new C−C bond was created, leading the bicyclic compound **3j** with the phenyl group in an equatorial position (Scheme 3).

Scheme 2. Oxazolidin-2-one Ring-Opening: From *N*-Benzyl-5-benzyloxazolidin-2-one 3i to Amino Alcohol 4



Scheme 3. Rationalization of the Configuration of the Major Diastereomer of 3j through the Iodo Cyclization/Cross-Coupling Sequence

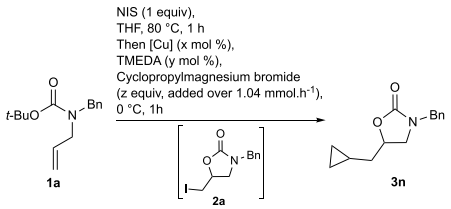


As a compound has a better chance to be on the market by "escaping from flatland",[20] the replacement of an aryl group at the C5′ position of the oxazolidin-2-ones by an aryl bioisostere, such as cyclopropane, has been envisaged. Thus, *N*-Boc-*N*-benzylallylamine **1a** was treated, under the previously optimized reaction conditions, with cyclopropylmagnesium bromide. However, the use of Co(acac)$_3$, as well as other cobalt or iron salts was not effective as **3n** was not formed (see Table S3). Due to this failure, the use of copper salts was explored to realize the coupling between the iodo-oxazolidin-2-one **2a**, intermediately formed, and cyclopropylmagnesium bromide (1.2 equiv, rate of addition v = 1.04 mmol.h^{-1}, 0 °C, 1 h) (Table 4). Different copper salts were screened such as Li_2CuCl_4 (10 mol %) and $CuCl_2$ (10 mol %); however, these catalysts did not produce the desired oxazolidin-2-one **3n** (Table 4, entries 1 and 2). On the contrary, when CuI (10 mol %) was utilized, the oxazolidin-2-one **3n** was formed in 31% yield (^{1}H NMR yield) (Table 4, entry 3). Increasing the excess of cyclopropylmagnesium bromide from 1.2 to 3 equiv led to **3n** in 53% yield (^{1}H NMR yield) (Table 4, entry 4). Adding TMEDA (40 mol %) to the reaction mixture allowed the full conversion of **2a** to **3n** which was obtained in 64% yield (^{1}H NMR yield) (Table 4, entry 5). Decreasing the catalytic loading of CuI from 10 to 5 mol % in the presence of TMEDA

https://dx.doi.org/10.1021/acs.orglett.0c01114
Org. Lett. XXXX, XXX, XXX−XXX

(40 mol %) afforded **3n**, which was isolated in 66% yield (Table 4, entry 6). It is worth mentioning that the catalytic loading of CuI can be decreased from 5 to 2.5 mol % in the presence of TMEDA (40 mol %) as **3n** was obtained in a similar yield (64%, ^{1}H NMR yield) (Table 4, entry 7).

Table 4. Optimization of the Reaction Conditions for the Cross-Coupling in a One-Pot Sequence to Access Oxazolidin-2-one 3n from *N*-Boc-*N*-Benzylallylamine 1a Using Cyclopropylmagnesium Bromide



entry	[Cu] (x mol %)	TMEDA (y mol %)	cyclopropylmagnesium bromide (z equiv)	**3n**[a] (%)
1	Li_2CuCl_4 (10)	none	1.2	none
2	$CuCl_2$ (10)	none	1.2	traces
3	CuI (10)	none	1.2	31
4	CuI (10)	none	3	53
5	CuI (10)	40	3	64
6	CuI (5)	40	3	66[b]
7	CuI (2.5)	40	3	64

[a] ^{1}H NMR yield determined by using 1,3-dimethoxybenzene as internal standard. [b] Isolated yield.

In summary, we developed a one-pot sequence of reactions involving an iodo-cyclization/cross-coupling to produce a diversity of C5-functionalized oxazolidin-2-ones from simple *N*-Boc-allylamines. For the cross-coupling, depending on the aryl or cyclopropyl Grignard reagents involved in the process, Co or Cu salts have to be used for the success of the coupling. Moreover, this sequence of reactions allowed the access to bicyclo- and spiro-heterocycles with good diastereoselectivities and 1,2-amino alcohols can be obtained by simple ring-opening of the oxazolidin-2-ones. This scalable one-pot two-step sequence appears to be a useful tool and paves the way for promising Csp^3–Csp^2 and Csp^3–Csp^3 cross-couplings, catalyzed by earth-abundant transition metals, to access functionalized heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01114.

Experimental procedures and spectral data for all compounds (PDF)

Accession Codes

CCDC 1991426–1991427 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Janine Cossy − *Molecular, Macromolecular Chemistry and Materials, ESPCI Paris, PSL University, CNRS, 75005 Paris, France;* orcid.org/0000-0001-8746-9239; Email: janine.cossy@espci.fr

Author

Pauline Chaumont-Olive − *Molecular, Macromolecular Chemistry and Materials, ESPCI Paris, PSL University, CNRS, 75005 Paris, France;* orcid.org/0000-0002-4137-3079

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01114

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–876. (c) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. *RSC Adv.* **2016**, *6*, 30498–30551. (d) Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; Rezende, D. C.; Alves Nogueira Diaz, M. *Chirality* **2019**, *31*, 776–812.

(2) Fugitt, R. B.; Luckenbaugh, R. W. 5-Halomethyl-3-phenyl-2-oxazolidinones. U.S. Patent 4,128,654, 1978.

(3) (a) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010–2023. (b) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529–542. (c) Barbachyn, M. R. Oxazolidinone Antibacterial Agents. In *Antibiotic Discovery and Development*; Dougherty, T., Pucci, M., Eds.; Springer: Boston, MA, 2012. (d) Song, L.; Chen, X.; Zhang, S.; Zhang, H.; Li, P.; Luo, G.; Liu, W.; Duan, W.; Wang, W. *Org. Lett.* **2008**, *10*, 5489–5492. (e) Michalska, K.; Karpiuk, I.; Król, M.; Tyski, S. *Bioorg. Med. Chem.* **2013**, *21*, 577–591. (f) Guo, B.; Fan, H.; Xin, Q.; Chu, W.; Wang, H.; Huang, Y.; Chen, X.; Yang, Y. *J. Med. Chem.* **2013**, *56*, 2642–2650. (g) Ghosh, A. K.; Brindisi, M. *J. Med. Chem.* **2015**, *58*, 2895–2940.

(4) Kalgutkar, A. S.; Dalvie, D. K.; Castagnoli, N.; Taylor, T. *Chem. Res. Toxicol.* **2001**, *14*, 1139–1162.

(5) (a) Somanathan, R.; Rivero, I. A.; Nuñez, G. I.; Hellberg, L. H. *Synth. Commun.* **1994**, *24*, 1483–1487. (b) Pramanik, C.; Bapat, K.; Patil, P.; Kotharkar, S.; More, Y.; Gotrane, D.; Chaskar, S. P.; Mahajan, U.; Tripathy, N. K. *Org. Process Res. Dev.* **2019**, *23*, 1252–1256.

(6) (a) Hitotsuyanagi, Y.; Hikita, M.; Uemura, G.; Fukaya, H.; Takeya, K. *Tetrahedron* **2011**, *67*, 455–461. (b) Gao, Y.; Wang, J.; Zhang, C.-F.; Xu, X. H.; Zhang, M.; Kong, L.-Y. *Tetrahedron* **2014**, *70*, 967–974. (c) Greger, H. *Phytochem. Rev.* **2019**, *18*, 463–493.

(7) Selected publications: (a) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197–246. (b) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727–2730. (c) Zappia, G.; Gacs-Baitz, E.; Monache, G. D.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Synth.* **2007**, *4*, 81–135. (d) Le Quement, S. T.; Flagstad, T.; Mikkelsen, R. J. T.; Hansen, M. R.; Givskov, M. C.; Nielsen, T. E. *Org. Lett.* **2012**, *14*, 640–643. (e) He, T.; Gao, W.-C.; Wang, W.-K.; Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 1113–1118. (f) Mahy, W.; Plucinski, P. K.; Frost, C. G. *Org. Lett.* **2014**, *16*, 5020–5023. (g) Derrien, N.; Sharley, J. S.; Rubtsov, A. E.; Malkov, A. V. *Org. Lett.* **2017**, *19*, 234–237. (h) Lebel, H.; Mamani Laparra, L.; Khalifa, M.; Trudel, C.; Audubert, C.; Szponarski, M.; Dicaire-Leduc, C.; Azek, E.; Ernzerhof, M. *Org. Biomol. Chem.* **2017**, *15*, 4144–4158. (i) McPherson, C. G.; Cooper, A. K.; Bubliauskas, A.; Mulrainey, P.; Jamieson, C.; Watson, A. J. B. *Org. Lett.* **2017**, *19*, 6736–6739. (j) Toda, Y.; Gomyou, S.; Tanaka, S.; Komiyama, Y.; Kikuchi, A.; Suga, H. *Org. Lett.* **2017**, *19*, 5786–5789. (k) Li, W.; Wollenburg, M.; Glorius, F. *Chem. Sci.* **2018**, *9*, 6260–6263.

(8) Selected publications: (a) Miller, A. W.; Nguyen, S.-B. T. *Org. Lett.* **2004**, *6*, 2301−2304. (b) Fontana, F.; Chen, C. C.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3454−3457. (c) Ghosh, A. K.; Brindisi, M. *J. Med. Chem.* **2015**, *58*, 2895−2940. (d) Macé, A.; Touchet, S.; Andres, P.; Cossío, F.; Dorcet, F.; Carreaux, F.; Carboni, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 1025−1029. (e) Lee, Y.; Choi, J.-H.; Kim, H. *Org. Lett.* **2018**, *20*, 5036−5039. (f) Boddy, A. J.; Cordier, J. C.; Goldberg, K.; Madin, A.; Spivey, A. C.; Bull, A. J. *Org. Lett.* **2019**, *21*, 1818−1822. (g) Niemi, T.; Repo, T. *Eur. J. Org. Chem.* **2019**, 1180−1188. (h) Wang, S.; Xi, C. *Chem. Soc. Rev.* **2019**, *48*, 382−404. (i) Yousefi, R.; Struble, T. J.; Payne, J. L.; Vishe, M.; Schley, N. D.; Johnston, J. N. *J. Am. Chem. Soc.* **2019**, *141*, 618−625. (j) Zhao, X.; Yang, S.; Ebrahimiasl, S.; Arshadi, S.; Hosseinian, A. *Journal of CO2 Utilization* **2019**, *33*, 37−45.

(9) (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492. (b) Cahiez, G.; Moyeux, A.; Cossy, J. *Adv. Synth. Catal.* **2015**, *357*, 1983−1989. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587−9652. (d) Barde, E.; Guérinot, A.; Cossy, J. *Synthesis* **2019**, *51*, 178−184.

(10) Selected publications for cobalt-catalyzed cross-coupling: (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137−4139. (b) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. - Eur. J.* **2004**, *10*, 5640−5648. (c) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207−2213. (d) Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484−1488. (e) Gosmini, C.; Beǵouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221−3233. (f) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277−280. (g) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435−1462. (h) Hsu, S.-F.; Ko, C.-W.; Wu, Y.-T. *Adv. Synth. Catal.* **2011**, *353*, 1756−1762. (i) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945−4949. (j) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 17662−17668. (k) Kuzmina, O. M.; Steib, A. K.; Fernandez, S.; Boudot, W.; Markiewicz, J. T.; Knochel, P. *Chem. - Eur. J.* **2015**, *21*, 8242−8249. (l) Pal, S.; Chowdhury, S.; Rozwadowski, E.; Auffrant, A.; Gosmini, C. *Adv. Synth. Catal.* **2016**, *358*, 2431−2435. (m) Hammann, J. M.; Hofmayer, M. S.; Lutter, F. H.; Thomas, L.; Knochel, P. *Synthesis* **2017**, *49*, 3887−3894. (n) Barré, B.; Gonnard, L.; Guérinot, A.; Cossy, J. *Molecules* **2018**, *23*, 1449−1460.

(11) Selected publications for copper-catalyzed cross-coupling: (a) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733−2737. (b) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086−2089. (c) Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1278−1281. (d) Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 9110−9113. (e) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124−11127. (f) Thapa, S.; Shrestha, B.; Gurung, S. K.; Giri, R. *Org. Biomol. Chem.* **2015**, *13*, 4816−4827. (g) Dai, W.; Shi, H.; Zhao, X.; Cao, S. *Org. Lett.* **2016**, *18*, 4284−4287.

(12) Selected publications for nickel-catalyzed cross-coupling: (a) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602−1604. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222−4223. (c) Guo, W.-J.; Wang, Z.-X. *J. Org. Chem.* **2013**, *78*, 1054−1061. (d) Tarui, A.; Kondo, S.; Sato, K.; Omote, M.; Minami, H.; Miwa, Y.; Ando, A. *Tetrahedron* **2013**, *69*, 1559−1565. (e) Tarui, A.; Miyata, E.; Tanaka, A.; Sato, K.; Omote, M.; Ando, A. *Synlett* **2014**, *26*, 55−58. (f) Fache, F.; Pelotier, B.; Piva, O. *Phys. Sci. Rev.* **2016**, *1*, 20160033.

(13) Selected publications for iron-catalyzed cross-coupling: (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609−611. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299. (c) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (d) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500−1511. (e) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773−8787. (f) Sherry, B. D.; Fürstner, A. *Chem. Commun.* **2009**, 7116−7118. (g) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945−4949. (h) Kuzmina, O. M.; Steib, A. K.; Fernandez, S.; Boudot, W.; Markiewicz, J. T.; Knochel, P. *Chem. - Eur. J.* **2015**, *21*, 8242−8249. (i) Kuzmina, O. M.; Steib, A. K.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synthesis* **2015**, *47*, 1696−1705. (j) Piontek, A.; Bisz, E.; Szostak, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11116−11128. (k) Kim, J. G.; Baek, J. H.; Kim, Y. J.; Jang, Y. J.; Kang, E. J. *Asian J. Org. Chem.* **2019**, *8*, 1648−1653. (l) Cahiez, G.; Lefèvre, G.; Moyeux, A.; Guerret, O.; Gayon, E.; Guillonneau, L.; Lefèvre, N.; Gu, Q.; Zhou, E. *Org. Lett.* **2019**, *21*, 2679−2683. (m) Li, Q.; Persoons, L.; Daelemans, D.; Herdewijn, D. *J. Org. Chem.* **2020**, *85*, 403−418. (n) Manjón-Mata, I.; Quirós, M. T.; Buñuel, E.; Cárdenas, D. J. *Adv. Synth. Catal.* **2020**, *362*, 146−151.

(14) (a) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101−11104. (b) Bensoussan, C.; Rival, N.; Hanquet, G.; Colobert, F.; Reymond, S.; Cossy, J. *Tetrahedron* **2013**, *69*, 7759−7770. (c) Nicolas, L.; Izquierdo, E.; Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S.; Cossy, J. *J. Org. Chem.* **2013**, *78*, 11807−11814. (d) Barre, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett.* **2014**, *16*, 6160−6163. (e) Gonnard, L.; Guérinot, A.; Cossy, J. *Chem. - Eur. J.* **2015**, *21*, 12797−12803. (f) Guérinot, A.; Cossy, J. *Top. Curr. Chem.* **2016**, *374*, 49−122. (g) Barde, E.; Guérinot, A.; Cossy, J. *Org. Lett.* **2017**, *19*, 6068−6071. (h) Hostier, T.; Neouchy, Z.; Ferey, V.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2018**, *20*, 1815−1818. (i) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 6241−6244. (j) Andersen, C.; Ferey, V.; Daumas, M.; Bernardelli, P.; Guérinot, A.; Cossy, J. *Org. Lett.* **2019**, *21*, 2285−2289.

(15) Due to the scale-up of the reaction, the purification of one diastereomer, **3m**, was more difficult on large scale than on small scale (22% on large scale and 31% on small scale).

(16) Haftchenary, S.; Nelson, S. D., Jr; Furst, L.; Dandapani, S.; Ferrara, S. J.; Boskovic, Z. V.; FigueroaLazu, S.; Guerrero, A. M.; Serrano, J. C.; Crews, D. K.; Brackeen, C.; Mowat, J.; Brumby, T.; Bauser, M.; Schreiber, S. L.; Phillips, A. J. *ACS Comb. Sci.* **2016**, *18*, 569−574.

(17) Martin, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 93−95.

(18) Deshmukh, S. C.; Roy, A.; Talukdar, P. *Org. Biomol. Chem.* **2012**, *10*, 7536−7544.

(19) (a) Isaac, M.; Slassi, A.; Egle, I.; Clayton, J. WO 2008/032191A2, 2008. (b) Meese, C.; Selve, N.; Schmidt, D. US 7,282,515B2, 2007.

(20) (a) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712−8756. (b) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752−6756. (c) Lovering, F. *MedChemComm* **2013**, *4*, 515−519.

https://dx.doi.org/10.1021/acs.orglett.0c01114
Org. Lett. XXXX, XXX, XXX−XXX