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Letter

## Stereospecific Iron-Catalyzed Carbon(sp<sup>2</sup>)–Carbon(sp<sup>3</sup>) Cross-Coupling with Alkyllithium and Alkenyl lodides

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**S** Supporting Information

ABSTRACT: An efficient synthetic protocol involving ironcatalyzed cross-coupling reactions between organolithium compounds and alkenyl iodides as key coupling partners was achieved. More than 30 examples were obtained with moderate to good yields and high stereospecificity. Gramscale and synthetic applications of this procedure are recorded herein to demonstrate its feasibility and potential utilization.

ransition-metal-catalyzed cross-coupling reactions for selective formation of C-C bonds enable facile preparations of various structurally diverse frameworks (Figure 1).<sup>1</sup> Although Murahashi and co-workers initially disclosed a palladium-catalyzed cross-coupling reaction of alkenyl halides with organolithium compounds in 1970,<sup>2</sup> a direct use of organolithium reagents in cross-coupling reactions had been neglected for a long time, mainly due to their high reactivity. In 2013, Feringa and co-workers developed palladium-based catalytic systems to directly generate C-C bonds using organolithium compounds as cross-coupling partners.<sup>3</sup> Thereafter, a series of nickel-catalyzed cross-coupling reactions were reported by Rueping, Uchiyama, and Feringa.<sup>4</sup> Nonetheless, due to the high cost, low natural abundance, and environmentally deleterious extraction and toxicity, there is a growing interest in replacing palladium/nickel-based catalysts with those more earth-abundant elements. Consequently, iron is a particularly attracting alternative. Therefore, development of iron-catalyzed cross-coupling is accordingly undergoing an explosive growth.<sup>5</sup>

In this context, Kochi pioneered an iron-catalyzed crosscoupling reaction in 1971.<sup>6</sup> Subsequently, the groups of Fürstner, Nakamura, Bedford, and Cahiez have all contributed significantly to iron-catalyzed cross-coupling reactions.<sup>7-</sup> Recently, our group developed an efficient iron-catalyzed cross-coupling protocol under mild conditions,<sup>11</sup> employing organolithium compounds and a variety of organic bromides. Our examples include formation of  $C(sp^2)-C(sp^3)$  bonds and  $C(sp^3)-C(sp^3)$  bonds, thereby providing a valuable alternative to existing methodologies by showing for the first time that organolithium reagents could be employed as cross-coupling partners in iron-catalyzed cross-coupling procedures. Subsequently, an efficient ligand-free iron-catalyzed cross-coupling reaction involving alkenyllithium and alkenyl iodides was also



a). Pd-catalyzed Cvinvl-Calkyl cross-coupling reaction



88% (99% isomeric purity)

b). Pd-catalyzed cross-coupling reaction with secondary alkyl lithiums



c). Ni-catalyzed dealkoxylative Caryl- Csp3 cross-coupling replacement

$$\begin{array}{c} OMe \\ R^3 \xrightarrow{\text{OW}} R^1 + Me_3Si \xrightarrow{\text{Li}} Li & \underbrace{\text{Ni}(cod)_2 (5 \text{ mol }\%)}_{\text{toluene, 60 °C, 2 h}} & R^3 \xrightarrow{\text{SiMe}_3} \\ R^1 \end{array}$$

d). Fe-catalyzed Caryl-Calkyl/Cvinyl-Cvinyl cross-coupling reactions



Figure 1. Transition-metal-catalyzed cross-coupling reactions to form a Č–C bond.

accomplished, leading to the formation of dienes in moderate to good yields.<sup>12</sup> Furthermore, our results also prompted us to uncover an efficient and selective approach to form alkenylalkyl

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derivatives using iron-catalyzed cross-coupling reactions between organolithium and alkenyl halides. Herein, we report a stereospecific method to form  $C(sp^2)-C(sp^3)$  bonds in moderate to good yields.

Our program began with (E)-2-iodovinylbenzene (1). Thus, compound 1 was allowed to react with 2 equiv of *n*-butyllithium without any iron catalyst or ligand. Disappointingly, only styrene was formed after the reaction, indicating that lithium-halide exchange occurred (Table 1, entry 1).

Table 1. Optimization

$\bigwedge$	<>' ⊥	Fe ca Lig	Ligand (5 mol %)		n-Bu	
		S	solvent,	23 °C		
1	additi	on over 2 h			1a	
entry	Fe	ligand	Li <sup>b</sup>	solvent	conv (%)	yield <sup>c</sup> (%)
1			2	PhMe	100	0
2	$Fe(acac)_3$		2	PhMe	66	22
3	FeCl <sub>3</sub>		2	PhMe	100	26
4	FeCl <sub>2</sub>		2	PhMe	93	9
5	$Fe(acac)_2$		2	PhMe	100	34
6	FeBr <sub>2</sub>		2	PhMe	100	22
7	$FeBr_3$		2	PhMe	100	20
8	$Fe(acac)_2$		2	THF	100	27
9	$Fe(acac)_2$		2	Et <sub>2</sub> O	100	17
10	$Fe(acac)_2$	$(\pm)$ -BINAP	2	PhMe	40	17
11	$Fe(acac)_2$	$(\pm)$ -BINAP	3	PhMe	100	52
12	$Fe(acac)_2$	$(\pm)$ -BINAP	4	PhMe	100	32
13	$Fe(acac)_2$	$SIMe \cdot HBF_4$	3	PhMe	100	60
14	$Fe(acac)_2$	SIMe·HCl	3	PhMe	100	42
15	$Fe(acac)_2$	PhDavePhos	3	PhMe	100	53
16	$Fe(acac)_2$	DavePhos	3	PhMe	100	$72^d$

<sup>*a*</sup>Reaction conditions: 0.2 mol of 1, 5 mol % of Fe catalyst, 5 mol % of ligand in 1 mL of solvent at room temperature. <sup>*b*</sup>The equiv of *n*-BuLi. <sup>*c*</sup>Determined by GC–MS. <sup>*d*</sup>Isolated yield.

With iron catalysts, cross-coupling product 1a, together with some homocoupling products, could be observed. A series of iron catalysts without ligand were screened (entries 2-7), and the highest yield of cross-coupling product was still 34% using  $Fe(acac)_2$ . Although different solvents were tested (entries 5, 8, and 9), no significant improvement resulted. It is noteworthy that, with the addition of a ligand  $(\pm)$ -BINAP, the conversion yield dropped to 40% and the product yield decreased correspondingly (entry 10), leading us to adjust the amount of *n*-butyllithium. Other experiments illustrated that, with 3 equiv of n-butyllithium, all starting materials were consumed and the cross-coupling yield was improved to 52%, while with 4 equiv of lithium reagent, the yield of 1a decreased to 32% instead, though the conversion yields were acceptable (entries 11-13). Then, several typical ligands including phosphine ligands and NHC ligands (Figure 2; other ligands' details can be seen in the Supporting Information) were screened. Relevant results showed that phosphine ligands seem to be much better for this system. Eventually, the best condition was found to be  $Fe(acac)_2$  and DavePhos, in which 72% of 1a was obtained (entry 16).

With the optimized reaction conditions in hand, we started to explore the substrate scope. Different alkyllithiums were examined first. The reaction results showed that all primary lithium reagents, such as methyllithium, *n*-hexyllithium,



Figure 2. Structures of ligands.

(trimethylsilyl)methyllithium, and isobutyllithium were well compatible under our conditions, leading to good yields (Scheme 1, 1b, 1c, 1d, and 1e). Secondary alkyllithium was

## Scheme 1. Scope of Alkyllithium



also compatible, but the cross-coupling yields slightly dropped (1f, 1g) compared to the relevant yields of primary lithium reagents.

On basis of the scope of various alkyllithiums in Scheme 1, we then turned our attention to the substrate scope. As shown Scheme 2, E-alkylvinyl iodides were tested. Electron-withdrawing groups, like -Br and -CF<sub>3</sub>, were introduced on the para-position of (E)-2-iodovinylbenzene (1). The expected cross-coupling products were also obtained with high yields under the same reaction condition. In addition, electrondonating groups such as the methoxy group were introduced on the meta-position, and it coupled with different alkyllithiums, resulting in high yields as well. Presumably, the electronic effect does not influence the reaction significantly, as compared with substrates 3a, 4a, and 5a. Other alkenyl iodides containing aromatic functional groups, such as 6, 7, and 8, all provided good yields. Likewise, 1,3-dipropenylbenzene (8a) (with 6 equiv of methyllithium) was also obtained in 97% yield. Furthermore, without a phenyl group, an alkylvinyl iodide was also examined, and as a result, 9a was obtained in 96% yield. In order to explore the reaction diversity, several examples with Z-alkenyl iodides were investigated. Thus, with different lithium reagents including primary and secondary lithium reagents, experimental results showed that these systems were well suited under our optimized conditions (11–15). Some products were even obtained with very high yields, such as 12a (93%) and 12b (81%). Moreover, regardless of yields, it is interesting to note that a very small percentage of isomerization was found in all cases, which supports our hypothesis that this reaction might likely not go through a radical pathway.<sup>13</sup> Finally, we examined some substrates with gem-vinyl iodide to widen the scope of our

### Scheme 2. Substrate Scope



approach. Interestingly, (iodovinyl)adamantane derivative 16, containing a significant steric hindrance, could also be coupled to form compounds 16a and 16b, though yields were much lower. In addition, two more substrates with cyclohexane moieties (15a and 17a) were achieved with moderate to high yields. Application of this protocol between the stanolone derivative 18 and methylithium successfully led to the desired moiety 18a in 82% yield.

We also confirmed the scalable feasibility of these ironcatalyzed reactions, as shown in Scheme 3. Several typical



scale-up reactions in multigram scales provided respective desired products in satisfactory yields. Moreover, to demonstrate the usefulness of this synthetic protocol, we subjected **2a** to some transformations, forming relevant epoxide **2aa**, bromide **2ab**, and 1,2,3-trisubstituted indane **2ac**, as shown in Scheme 4.<sup>14</sup>



To gain more insights into the reaction mechanism, additional studies were performed (Scheme 5). During the



cross-in coupling reaction of substrate 2, a known radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), was added to the reaction mixture under standard conditions. It was found that the yield of 2a was dramatically decreased (Scheme 5a, 0% vs 82% Scheme 2). Moreover, when 20% of TEMPO was added, the yield of 2a dropped to 50% rather than 0%, as compared with 100% of TEMPO. In both experiments, the TEMPO-*n*-Bu adduct was observed by GC–

MS. However, these results did not necessarily indicate that this reaction went through a radical pathway, in comparison to control experiments (Scheme 5b). It is clear that substrate 2a cannot react with TEMPO, but the other reagent, nbutyllithium could be coupled with TEMPO directly even without any iron catalysts. Combined with our previous experiments (Schemes 5a,b), there is therefore no clear evidence to support the notion that the decreasing yield is caused by the trapped radical or the insufficient lithium reagents. Furthermore, the reaction of 10 was carried out and monitored very carefully (Scheme 5c), but only trace isomerization product 1c was observed (Z/E > 15:1). On the other hand, radical clock experiments of 19 and 20 were also performed. The results indicated that no ring-closing product 19a or ring-opening product 20a was observed, therefore hinting at the absence of transient radical intermediates (Scheme 5d). These studies suggested that radical pathways were not likely to be involved in this reaction.

In conclusion, an effective stereospecific Fe(II)-catalyzed alkenylalkyl cross-coupling reaction was developed. More than 30 examples were obtained with moderate to good yields. The reaction can be scaled up to gram scale, and further transformations of the iron-catalyzed cross-coupling reaction products were explored. The plausible reaction mechanism was proposed on the basis of our controlled experiments and preliminary investigations (see the Supporting Information).

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00394.

Experimental procedures, product characterization data (PDF)

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## Notes

The authors declare no competing financial interest.

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