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A Novel Iron-Catalyzed Decarboxylative Csp^3-Csp^2 Coupling of Proline Derivatives and Naphthol

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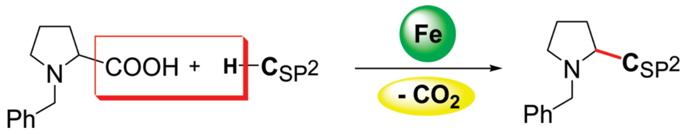
ABSTRACT



A novel iron-catalyzed intermolecular decarboxylative Csp^3-Csp^2 coupling reaction using proline derivatives as starting materials is developed. In this process, a series of potentially useful ligands (tertiary aminonaphthol) for catalysis was obtained.

Transition-metal-catalyzed decarboxylative couplings hold considerable promise among novel carbon−carbon bond formations owing to their potential advantages, such as high efficiency, selectivity, and convenience.[1,2] For example, the groups of Goossen,[3] Myers,[4] and Tunge[5] have reported transition-metal-catalyzed intermolecular and intramolecular decarboxylative couplings. A large number of useful strategies for the formation of C−C bonds and practical building blocks were obtained. However, this field is largely dominated by the use of palladium complexes, and there is a limitation of the availability of appropriate substrates for such reactions.[3−6] α-Amino acids are easily accessible, simple, and stable molecules. They are among the most attractive synthons for the construction of amine compounds. As a result, they have attracted much attention in industrial and academic research due to their biological and pharmaceutical properties.[7] Recently, we have developed a wide range of C−C bond formation reactions to synthesize amine deriva-

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[†] McGill University.

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(1) For some recent examples of decarboxylative reaction, see: (a) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944–2945. (b) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852–2853. (c) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440–11441. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181. (e) Bourgeois, D.; Craig, D.; King, N. P.; Mountford, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 618–621. (f) Craig, D.; Grellepois, F. *Org. Lett.* **2005**, *7*, 463–465. (g) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (h) Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991–6995. (i) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879–2882. (j) Sim, S. H.; Park, H.-J.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2008**, *10*, 433–436. (k) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.- L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738–5739.

(2) For a review, see: Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100–3120.

(3) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664. (b) Gooβen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833. (c) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043–3045. (d) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103–7106.

(4) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433–436. (c) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333.

(5) (a) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511. (b) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977–4980. (c) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002–10003. (d) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138–4139. (e) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860–14861. (f) Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657–4660.

(6) (a) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469–483. (b) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537–1539. (c) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495–2498. (d) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945–948.

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tives based on cross-dehydrogenative coupling (CDC).[8] However, a limitation of such methods is the challenge in controlling the regioselectivity of the C−H bonds. Alternatively, the carboxylic group of α-amino acids provides the possibility for site-specific functionalization of an α-amino acid skeleton using decarboxylative coupling reactions to generate amine products. With this notion in mind, very recently we have developed a C−C bond-forming reaction based on a copper-catalyzed oxidative decarboxylative coupling of sp^3-hybridized carbons of α-amino acids.[9] Despite the efficiency of the copper-catalyzed method in alkynylation and indolation, the attachment of other compounds such as naphthaol and phenols is not effective under such reaction conditions. Thus, an alternative catalytic system is desirable both to make the method even less expensive as well as to extend the scope of this methodology, in particular, to naphthols and phenols to generate novel aminonaphthol ligands (ligands of our interests for asymmetric synthesis).[10] Iron catalysis appears to provide many opportunities in this regard, because iron compounds are generally nontoxic, environmentally benign, cheap, and readily available (the second most abundant metal in the earth crust). Also, there are often complementary reactivities between copper and iron. Recently, iron has been applied in the cross-coupling of arenes with Grignard reagents,[11−13] and bioactive natural products[14,15] have also been synthesized successfully via iron catalysis. Very recently, Vogel also reported an iron-catalyzed desulfinylative C−C cross-coupling reaction of sulfonyl chlorides with Grignard reagents.[16] To the best of our knowledge, however, there have been no reports on the decarboxylative coupling by iron catalysis. Herein, we report an efficient and practical reaction system for the iron-catalyzed Csp^3−Csp^2 decarboxylative coupling.

Initial experiments were performed using proline **1a**, 1.5 equiv of *β*-naphthol (**2a**), and 1.5 equiv of *tert*-butyl peroxide (**4a**), together with 10 mol % of $FeCl_2$ as the catalyst in toluene at 115 °C under argon overnight (Table 1, entry 1). The desired tertiary amino-naphthol product **3a** was obtained in 70% yield. To improve the yield, different catalysts were examined, and $FeSO_4$ gave the best yield compared with other iron catalysts (entries 3−5). The attempts with other oxidants, such as dicumyl peroxide and TBHP (*t*BuOOH) led to lower yields of the desired product (entries 7 and 8). However, when racemic ligand *trans*-1,2-diaminocyclohexane was used, excellent yields were obtained (entries 2 and 6). Later, it was found that the ratio of the starting materials was important to obtain high yields of the product. When 1.0 equiv of *β*-naphthol (**2a**) and 1.5 equiv of proline **1a** were used, an excellent yield was obtained (entry 9). The use of 1.2 equiv of proline **1a** gave a slightly lower yield of the aminonaphthol product (entry 10). If there was no iron catalyst, only 31% yield was obtained (entry 11). And in all cases, under the examined oxidative reaction conditions, only a small amount of BINOL was formed (Table 1).

The efficient formation of coupling products prompted us to study the reaction scope further. As shown in Table 2, the bromine group on the *β*-naphthol was tolerated by the iron-catalyzed reaction (entry 2). *β*-Naphthol bearing an electron-donating group at the C_6 and C_7 positions reacted smoothly to give the corresponding products in good yields (entries 3 and 4). Meanwhile, the use of *N*-benzylproline containing a chlorine substituient at the *meta*-position also gave good results (enties 5−7). When α-amino acid **1c**

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(7) (a) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253–3254. (b) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521–6524.

(8) For selected references, see: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999. (c) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928–8933. (d) Zhao, L.; Basle, O.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4106–4111. (e) For an account, see: Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (f) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935–945.

(9) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792–795.

(10) (a) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590–597. (b) MacLeod, P. D.; Li, Z.; Feng, J. Q.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 6791–6794. (c) Feng, J. Q.; Bohle, S. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2007**, *18*, 1043–1047. (d) Feng, J.; Dastgir, S.; Li, C.-J. *Tetrahedron Lett.* **2008**, *49*, 668–671.

(11) For reviews on iron catalysis, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, 624–629. (c) Díaz, D. D.; Miranda, P. O.; Padrón, J. I.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 457–476. (d) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321. (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511. (f) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341–1369. (g) Gaillard, S.; Renaud, J.-L. *ChemSusChem* **2008**, *1*, 505–509. (h) Correa, A.; García Manchenõ, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (i) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364–1367.

(12) (a) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205. (b) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901–1904. (c) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609–612. (d) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (e) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949. (f) Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015–1018.

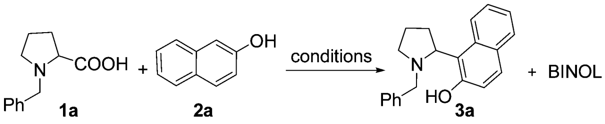
(13) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (c) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957. (d) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822–2823. (e) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654–1658. (f) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161–4163. (g) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104–1110. (h) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733–735. (i) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364–4366. (j) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844–9845.

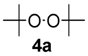
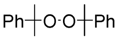
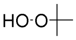
(14) (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308–311. (b) Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960–11965. (c) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358–5360. (d) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971. (e) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462–3466. (f) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204. (g) Fürstner, A.; De Souza, D.; Turet, L.; Fenster, M. D. B.; Parra-Rapado, L.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chem.−Eur. J.* **2007**, *13*, 115–134. (h) Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aïssa, C.; De Souza, D.; Nevado, C.; Tuttle, C. T. T.; Thiel, W.; Müller, O. *Chem.−Eur. J.* **2007**, *13*, 135–149. (i) Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aïssa, C.; De Souza, D.; Müller, O. *Proc. Natl. Acad. Sci. U.S.A* **2005**, *102*, 8103–8106. (j) Fürstner, A.; Hannen, P. *Chem.−Eur. J.* **2006**, *12*, 3006–3019.

(15) For other applications in synthesis, see: (a) Hamajima, A.; Isobe, M. *Org. Lett.* **2006**, *8*, 1205–1208. (b) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969. (c) Dickschat, J. S.; Reichenbach, H.; Wagner-Döbler, I.; Schulz, S. *Eur. J. Org. Chem.* **2005**, 4141–4153. (d) Hocek, M.; Dvoøáková, H. *J. Org. Chem.* **2003**, *68*, 5773–5776. (e) Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962–3967.

(16) Rao Volla, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307.

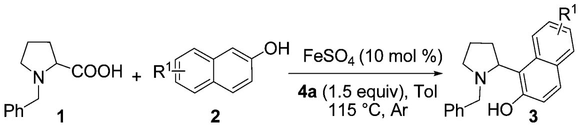
Table 1. Optimization of Reaction Conditions[a]

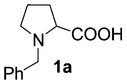
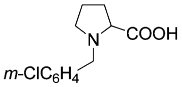
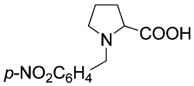


entry	1a (equiv)	2a (equiv)	catalyst	oxidant	NMR yield[b] (%)	BINOL yield[e] (%)
1	1.0	1.5	$FeCl_2$	 4a	70	6
2	1.0	1.5	$FeCl_2$	4a	98[c]	trace
3	1.0	1.5	$FeBr_2$	4a	68	8
4	1.0	1.5	$FeSO_4$	4a	80	trace
5	1.0	1.5	$FeCl_3$	4a	50	8
6	1.0	1.5	$FeCl_3$	4a	95[c]	trace
7	1.0	1.5	$FeSO_4$		65	trace
8	1.0	1.5	$FeSO_4$		54	trace
9	1.5	1.0	$FeSO_4$	4a	100[d]	trace
10	1.2	1.0	$FeSO_4$	4a	95[d]	trace
11	1.5	1.0	-	4a	31	trace

[a] Reactions were carried out on a 0.2 mmol scale in toluene (1.0 mL) under argon at 115 °C overnight with oxidant (1.5 equiv) and catalyst (0.10 equiv). [b] Reported yields were based on **1a** and determined by NMR methods using an internal standard. [c] *trans*-1,2-Diaminocyclohexane (0.30 equiv) was used. [d] Reported yields were based on **2a**. [e] Isolated yields were based on **2a**.

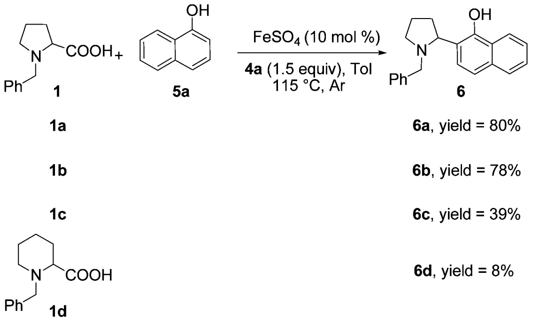
Table 2. Decarboxylative Csp^3-Csp^2 Coupling[a]



entry	1	R1		product	yield[b] (%)
1	 **1a**		**2a**	**3a**	100(78)
2	**1a**	6-Br	**2b**	**3b**	60(43)
3	**1a**	6-OMe	**2c**	**3c**	78(59)
4	**1a**	7-OMe	**2d**	**3d**	91(74)
5	 **1b**		**2a**	**3e**	86(68)
6	**1b**		**2b**	**3f**	86(74)
7	**1b**		**2c**	**3g**	90(66)
8	 **1c**		**2a**	**3h**	55(45)
9	**1c**		**2b**	**3i**	47(31)
10	**1c**		**2c**	**3j**	50(32)

[a] **1** (1.5 equiv), **2** (1.0 equiv), **4a** (1.5 equiv), and $FeSO_4$ (10 mol %) in toluene (1.0 mL). [b] NMR yields are based on β-naphthol and determined by NMR using an internal standard; isolated yields are given in parentheses.

Scheme 1. Decarboxylative Coupling of α-Naphthol



bearing a nitro group at the *para*-position was employed, moderate yields were obtained (enties 8−10).

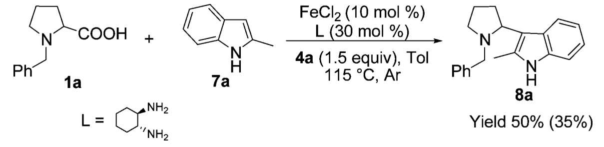
To our delight, when α-naphthol **5a** was used as the substrate the reaction proceeded smoothly under the same conditions and afforded the coupling product **6a**. The results are summarized in Scheme 1. Different proline derivatives could be applied to this coupling reaction readily, and moderate to good isolated yields were obtained in all cases. For six-membered ring α-amino acid **1d**, however, the desired product was obtained in a lower yield.

When changing the nucleophile to indole, the desired product **8a** was obtained in 50% NMR yield (35% isolated yield) employing 1.0 equiv of proline **1a** and 1.5 equiv of indole **7a** using $FeCl_2$ as catalyst together with racemic ligand *trans*-1,2-diaminocyclohexane (Scheme 2). Subsequently, an attempt was made to generate optically active products by using optically pure (*R*,*R*)-*trans*-1,2-diaminocyclohexane as a ligand, which resulted in only racemic products. The use of $FeSO_4$ gave very low yield in this case.

The proposed mechanism for this decarboxylative coupling is shown in Scheme 3. Oxidative decarboxylation of amino acid derivative **1** initiated by iron and oxidant first generated the imine-type intermediate **9**.[9,17] Then the intermediate **9** coordinated with iron and intermediate **10** was formed. Finally, the coupling of **10** with nucleophile afforded the coupling products and regenerated the iron catalyst for further reaction.

In summary, a novel Fe-catalyzed decarboxylative Csp^3-Csp^2 coupling reaction was developed using proline derivatives (readily available substrates). In this process, a broad range of potential ligands (tertiary aminonaphthol) for organic syntheses can be readily accessible. The scope,

Scheme 2. Decarboxylative Coupling of Proline **1a** and Indole



mechanism, and synthetic application of this reaction are under investigation.

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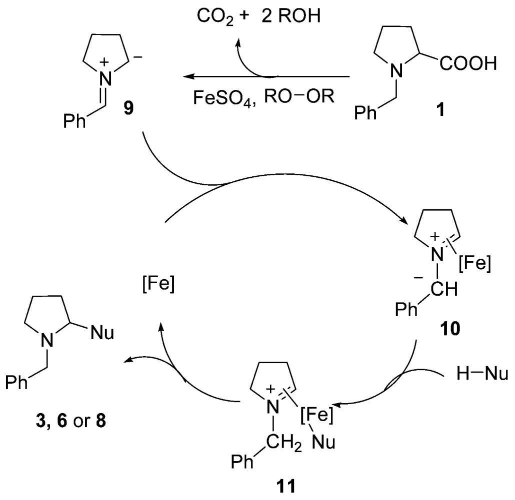
---

(17) For oxidative decarboxylations of amino acids, see: (a) Gowda, B. T.; Mahadevappa, D. S. *J. Chem. Soc., Perkin Trans. 2* **1983**, 323–334. (b) Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1985**, *50*, 1206–1212. (c) Itoh, S.; Mure, M.; Suzuki, A.; Murao, H.; Ohshiro, Y. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1245–1251. (d) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170–6172. (e) Takeda, T.; Yamauchi, S.; Fujiwara, T. *Synthesis* **1996**, 600–602. (f) Boto, A.; Hernandez, R.; De Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803. (g) Zabinski, R. F.; Toney, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 193–198. (h) Liu, L.; Zhou, W.; Chruma, J.; Breslow, R. *J. Am. Chem. Soc.* **2004**, *126*, 8136–8137. (i) Huang, W. H.; Wang, M. L.; Yue, H. *Synthesis* **2008**, 1342–1344.

Scheme 3. Proposed Mechanism for Fe-Catalyzed Decarboxylative Coupling



Supporting Information Available: Typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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