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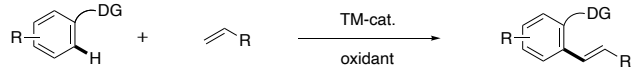
Abstract. The dehydrogenative coupling of aromatic amides with dimethyl itaconate proceeds smoothly under rhodium catalysis through *ortho* C–H bond cleavage directed by their amide group to produce benzylidenesuccinates. Aromatic carboxylic acids including benzoic and phthalic acids also couple with the itaconate to give 1:2 coupling products predominantly. Benzylidenesuccinic acid derivatives have been known to show various biological activities. These reactions provide easy access to the important structures.

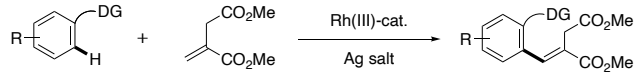
Benzylidenesuccinic acids and their derivatives have been of interest because of their biological activities.[1] Furthermore, they have also drawn attention for their utility as synthetic intermediates on the ways toward functional molecules and natural products.[2] Especially, they undergo asymmetric addition of hydrogen[3] and amines[4] to produce chiral benzylsuccinic acids as well as amino acids. Benzylidenesuccinates used to be prepared via classical condensations and Wittig-type reactions.[5] Later, Mizoroki-Heck-type arylation of itaconates have become utilized for the synthesis of variously substituted benzylidenesuccinates.[6] Itaconic acid and its derivatives have been recognized as promising building-blocks due to their ready availability and renewability.[7] Actually, they can be provided by industrial fermentation of carbohydrates. Compared with the conventional cross-coupling method, the transition-metal-catalyzed direct coupling of aromatic substrates with itaconates through arene C–H bond cleavage is undoubtedly attractive from the atom- and step-economic points of view.[8] The dehydrogenative coupling with alkenes has been referred to as C–H alkenylation and employed for the straightforward synthesis of arylalkenes (Scheme 1a).[9] Monosubstituted alkenes are usually used in most cases of such reaction. In contrast, the reaction with 1,1-disubstituted alkenes such as itaconates has been relatively less explored. In the context of our study on C–H alkenylation,[10] we have found that the dehydrogenative coupling of aromatic amides and carboxylic acids with dimethyl itaconate proceeds smoothly under rhodium catalysis through ortho C–H bond cleavage directed by amide and carboxy functions and disubstituted C=C double bond insertion (Scheme 1b). The procedure provides straightforward synthetic pathways toward a series of benzylidenesuccinates from readily available starting materials. The new findings are described herein.

a) TM-catalyzed C–H alkenylation



DG = N-, O-, P-, S-containing directing group

b) This work

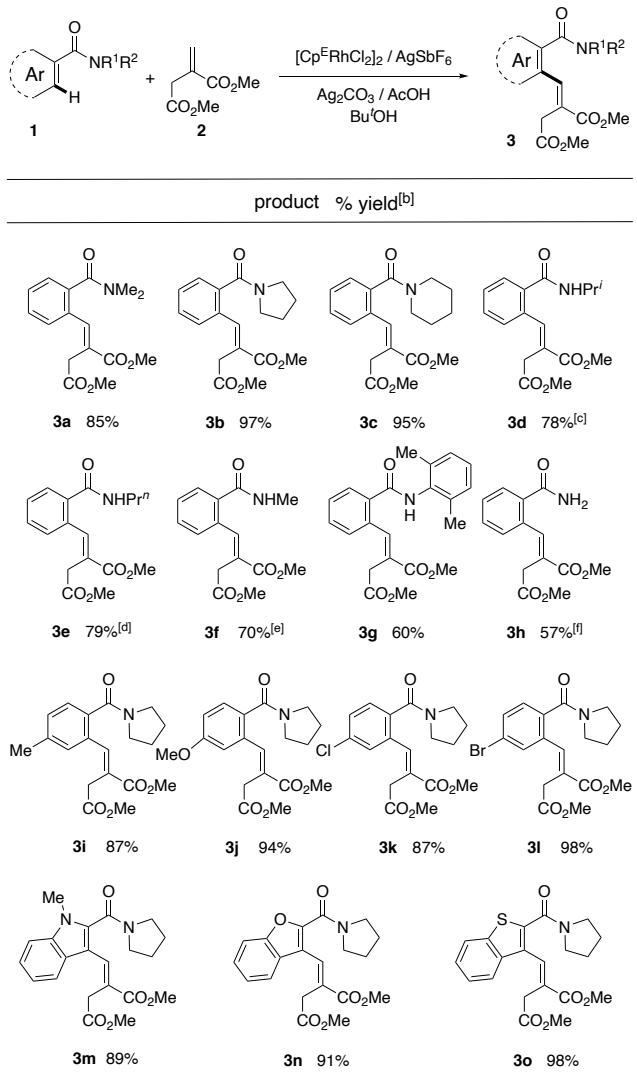


DG = $CONR^1R^2$, CO_2H, NHCOMe

Scheme 1. Dehydrogenative Coupling of Aromatic Substrates with Alkenes.

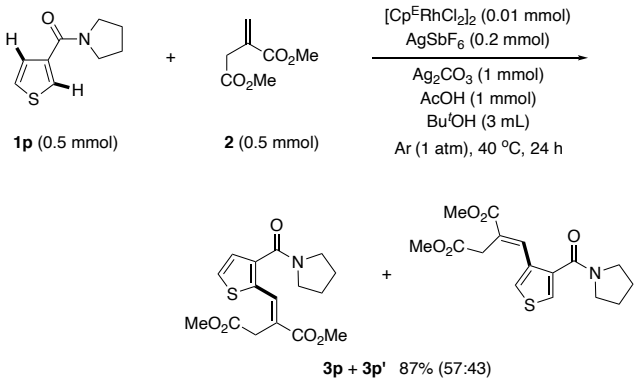
Previously, we have reported[11] that the dehydrogenative coupling of benzamides with another kind of 1,1-disubstituted alkene, methyl 2-trifluoromethylacrylate, can be conducted efficiently in the presence of a catalyst system $[Cp^ERhCl_2]_2$[12] / $AgSbF_6$ and Ag_2CO_3 as oxidant. Therefore, in an initial attempt, *N*,*N*-dimethylbenzamide (**1a**) (0.5 mmol) was treated with dimethyl itaconate (**2**) (0.5 mmol) in the presence of $[Cp^ERhCl_2]_2$ (0.01 mmol, 2 mol %), $AgSbF_6$ (0.2 mmol), Ag_2CO_3 (1 mmol), and AcOH (1 mmol) in Bu^{t}OH under Ar (1 atm) at 40 °C for 24 h. As a result, dimethyl (*E*)-2-(2-(dimethylcarbamoyl)benzylidene)succinate (**3a**) was obtained in 85% yield (Table 1). As in the previous Mizoroki-Heck type arylation of itaconates,[6] no geometric isomer ((*Z*)-**3a**) was detected by GC and GC-MS analyses for the reaction mixture. In the case using $[Cp^*RhCl_2]_2$ in place of $[Cp^ERhCl_2]_2$ as catalyst,[13] the **3a** yield considerably decreased (~10%). *N*-Benzoylpyrrolidine and -piperidine also

Table 1. Reaction of Aromatic Amides **1** with Itaconic Acid (**2**)[a].

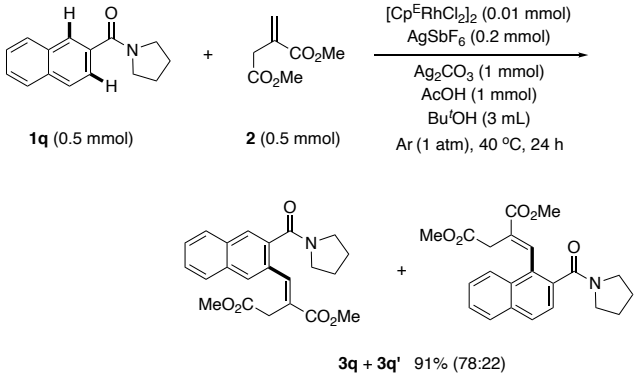


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $[Cp^ERhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.2 mmol), Ag_2CO_3 (1 mmol), AcOH (1 mmol) in Bu^{t}OH (3 mL) at 40 °C under Ar for 24 h. [b] Isolated yield based on the amount of **1** used. [c] 2,6-Dialkenylated product **4d** (9%) was also formed. [d] 2,6-Dialkenylated product **4e** (10%) was also formed. [e] 2,6-Dialkenylated product **4f** (6%) was also formed. [f] 2,6-Dialkenylated product **4h** (11%) was also formed.

underwent the dehydrogenative coupling with **2** to form **3b** and **3c**, respectively, in excellent yields. In addition to tertiary amides, secondary and primary benzamides could also be employed for the reaction. Thus, *N*-*i*-propyl, -*n*-propyl, and -methylbenzamides reacted with **2** smoothly to produce **3d**-**f** in 70-79% yields. In these cases, minor amounts (6-10%) of 2,6-dialkenylated products **4d**-**f** were also detected. The reaction of a more sterically hindered benzamide, *N*-(2,6-dimethylphenyl)benzamide, gave only a monoalkenylated product **3g** in 60% yield. In contrast, less hindered *N*-unsubstituted benzamide reacted with **2** to form mono- (**3h**) and dialkenylated products (**4h**) in 57 and 11% yields, respectively. Next, the reactions of various aroyl- and heteroaroylpyrrolidines with **2** were examined. 4-Methyl, -methoxy, -chloro, and -bromo substituted benzoylpyrrolidines underwent the mono-alkenylation to form **3i-l** in 87-98% yields. The dehydrogenative coupling of (1-methyl-1*H*-indol-2-yl)-, (benzo[*b*]furan-2-yl)-, and (benzo[*b*]thiophen-2-yl)(pyrrolidin-1-yl)methanones with **2** took place at their C3 positions to produce **3m**-**o** in good yields. In contrast, the reaction of pyrrolidin-1-yl(thiophen-3-yl)methanone (**1p**) with **2** gave a mixture of C2- (**3p**) and C4-alkenylated products (**3p'**), as shown in Scheme 2. Similarly, in the reaction of *N*-naphtho-2-ylpyrrolidine (**1q**), a mixture of C3- (**3q**) and C1-alkenylated products (**3q'**) was formed (Scheme 3).



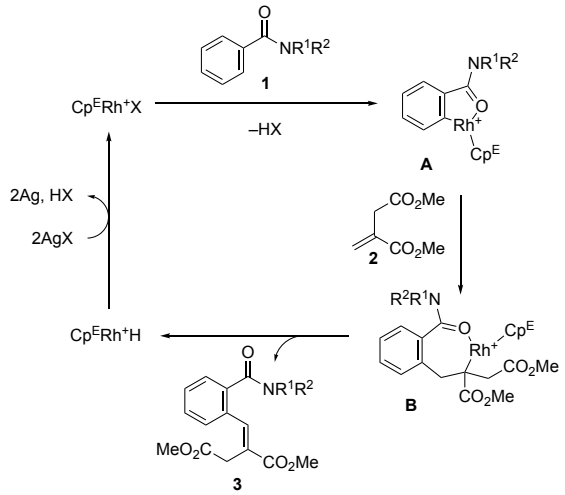
Scheme 2. Reaction of **1p** with **2**.



Scheme 3. Reaction of **1q** with **2**.

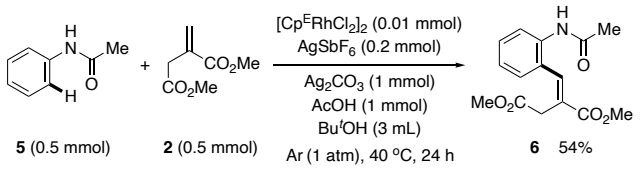
A plausible reaction pathway for the reaction of **1** with **2** are depicted in Scheme 4. Coordination of the amide function of **1** to a $Cp^ERh(III)$ species leads to regioselective C–H bond cleavage at the ortho position to give a five-membered rhodacycle intermediate **A**. Then, C=C double bond inertion of **2** and subsequent β-hydrogen elimination[14] from the resulting **B** may take place to produce **3**. Finally, an Rh(I) species generated from a hydridorhodium species seems to be reoxidized by an Ag salt to regenerate an active $Cp^ERh(III)$ species. In cases with sterically less crowded secondary and primary benzamides (R^1 and/or R^2 = H in Scheme 4), the second alkenylation

cycle at the C6-position seems to proceed, albeit with low efficiency.



Scheme 4. Plausible Mechanism for the Reaction of **1** with **2**.

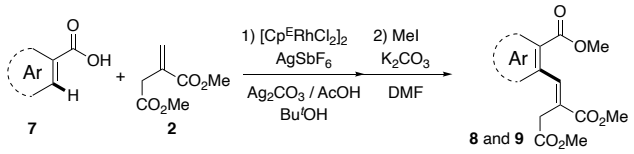
Besides benzamides, acetanilide (**5**)[15] also underwent the dehydrogenative coupling with **2** at the ortho-position under similar conditions to produce **6** in 54% yield (Scheme 5). Thus, the acetylamino moiety was shown to act as a directing group in our reaction system.



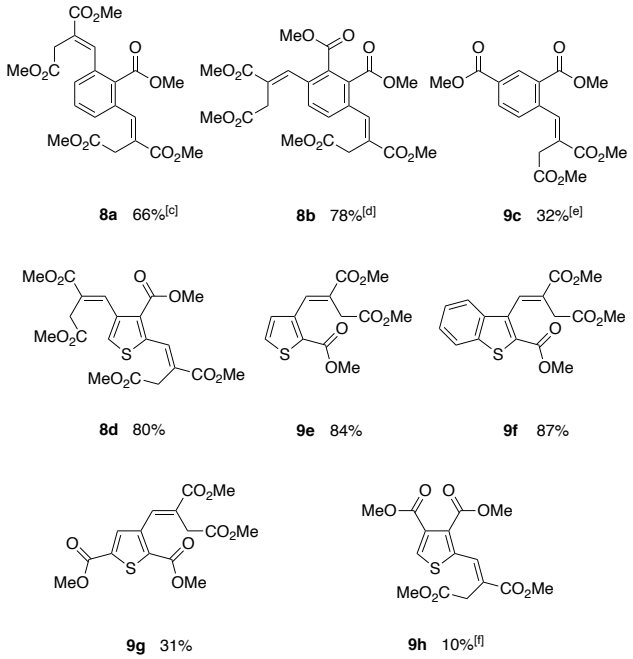
Scheme 5. Reaction of **5** with **2**.

Benzoic acids have been known to be good substrates for the rhodium(III)-catalyzed dehydrogenative coupling. Under Cp*Rh catalysis, ortho-unsubstituted benzoic acids usually undergo dialkenylation upon treatment with acrylates and styrenes.[16] Thus, benzoic acid (**7a**) was treated with three equivalents of **2** under the standard conditions, using a $[Cp^ERhCl_2]_2$ / $AgSbF_6$ catalyst system, Ag_2CO_3 oxidant, and AcOH additive in Bu^{t}OH under Ar (1 atm) at 40 °C for 24 h. After methyl esterification using MeI and K_2CO_3 for quantification, a dialkenylated product, tetramethyl 2,2'-((2-(methoxycarbonyl)-1,3-phenylene)bis(methaneylylidene))(2*E*,2'*E*)-disuccinate (**8a**), was obtained predominantly in 66% yield, along with a minor amount (10%) of monoalkenylated product **9a** (Table 2). Phthalic acid also underwent the reaction in a similar manner to give dialkenylated **8b** and monoalkenylated **9b** in 78 and 9% yields, respectively. The reaction of isophthalic acid was sluggish to produce monoalkenylated **9c** as a major product (32%) along with a minor amount (6%) of dialkenylated **8c**. Next, we examined the reactions of thiophene mono- and dicarboxylic acids. Thiophene-3-carboxylic acid reacted with **2** to afford dialkenylated product **8d** exclusively in 80% yield. The reactions of thiophene- and benzo[*b*]thiophene-2-carboxylic acid expectedly gave monoalkenylated **9e** and **9f,** respectively, in good yields. Thiophene-2,5- and -3,4-dicarboxylic acids underwent monoalkenylation at the C3- and C2-positions, respectively, albeit with low efficiency.

Table 2. Reaction of Aromatic Carboxylic Acids **5** with Itaconic Acid (**2**)[a]



product % yield[b]



[a] Reaction conditions: 1) **7** (0.5 mmol), **2** (1.5 mmol), $[Cp^ERhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.2 mmol), Ag_2CO_3 (1 mmol), AcOH (1 mmol) in Bu^{t}OH (3 mL) at 40 °C under Ar for 24 h. 2) With the addition of MeI (2.5 mmol), K_2CO_3 (1.5 mmol), and DMF (2 mL) at rt for 2 h. [b] Isolated yield based on the amount of **7** used. [c] 2-Monoalkenylated product **9a** (10%) was also formed. [d] 3-Monoalkenylated product **9b** (9%) was also formed. [e] 4,6-Dialkenylated product **8c** (6%) was also formed. [f] 2,5-Dialkenylated product **8h** (3%) was also formed.

In conclusion, we have demonstrated that aromatic amides and carboxylic acids undergo rhodium(III)-catalyzed dehydrogenative coupling with itaconate efficiently. This procedure enables to synthesize a variety of benzylidenesuccinates straightforwardly

from readily available starting materials. Work is underway for synthesizing more complicated polycarboxylic acid derivatives.

Experimental Section

Experimental Details: To a 30 mL two-necked flask with a reflux condenser, a balloon, and a rubber cup were added $[Cp^ERhCl_2]_2$ (0.01 mmol, 9 mg), $AgSbF_6$ (0.2 mmol, 69 mg), and Bu^{t}OH (3 mL). The mixture was stirred under air at room temperature for 15 min. Then, benzamide **1** (0.5 mmol), dimethyl itaconate (**2a**) (0.5 mmol, 79 mg), Ag_2CO_3 (1 mmol, 276 mg), AcOH (1 mmol, 60 mg), and 1-methylnaphthalene (ca. 50 mg) as internal standard were added and the resulting mixture was stirred under argon (1 atm) at 40 °C (bath temperature) for 24 h. After filtration through celite, the mixture was diluted with dichloromethane (40 mL). The organic layer was washed by 1 N HCl (40 mL), water (40 mL, twice), and brine (40 mL) and dried over Na_2SO_4. After removal of the solvents under vacuum, products **3** and **4** were purified by column chromatography on silica gel using hexane−ethyl acetate as eluent.

Acknowledgements

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Keywords: Amides; C-C coupling; C-H activation; Homogeneous catalysis; Rhodium

References

[1] For recent examples, see: a) H.-Y. Zhao, Q. Lan, S. He, B.-J. Su, Y.-Q. Wang, H.-B. Liao, H.-S. Wang, D. Liang, *Bioorg. Chem.* **2021**, *116*, 105332; b) J. Yang, J. Chen, Y. Hao, Y. Liu, *LWT-Food Sci. Technol*. **2021**, *146*, 111411; c) C. Shivanika, S. Deepak Kumar, V. Ragunathan, P. Tiwari, A. Sumitha, P. Brindha Devi, *J. Biomol. Struct. Dyn*. **2020**, Ahead of Print DOI: 10.1080/07391102.2020.1815584; d) P. Dixit, R. Chillara, V. Khedgikar, J. Gautam, P. Kushwaha, A. Kumar, D. Singh, R. Trivedi, R. Maurya, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 890.

[2] For example, see: a) B. L. Yvon, P. K. Datta, T. N. Le, J. L. Charlton, *Synthesis* **2001**, 1556; b) Y. Shi, J. G. Pierce, *Org. Lett.* **2016**, *18*, 5308.

[3] N. W. Boaz, E. B. MacKenzie, S. D. Debenham, S. E. Large, J. A. Ponasik, Jr., *J. Org. Chem*. **2005**, *70*, 1872.

[4] H. Raj, W. Szymański, J. de Villiers, H. J. Rozeboom, V. P. Veetil, C. R. Reis, M. de Villiers, F. J. Dekker, S. de Wildeman, W. J. Quax, A. M. W. H. Thunnissen, B. L. Feringa, D. B. Janssen, G. J. Poelarends, *Nat. Chem.* **2012**, *4*, 478.

[5] a) S. W. McCombie, C. A. Luchaco, *Tetrahedron Lett.* **1997**, *38*, 5775; b) A. F. Cameron, F. D. Duncanson, A. A. Freer, D. W. Armstrong, R. Ramage, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1030; c) W. S. Johnson, W. P. Schneider, *Org. Synth.* **1963**, *Coll. 4*, 132; d) H. Stobbe, *Ann.* **1899**, *308*, 89.

[6] a) L. Matelienė, J. Knaup, F. von Horsten, X. Gu, H. Brunner, *Eur. J. Org. Chem.* **2020**, 127; b) P. G. Bangar, P. R. Jawalkar, S. R. Dumbre, D. J. Patil, S. Iyer, *Appl. Organomet. Chem.* **2018**, *32*, e4159.

[7] Itaconic acid is known as one of bio-based platform chemicals. For a recent review, see: L. Regestein, T. Klement, P. Grande, D. Kreyenschulte, B. Heyman, T. Maßmann, A. Eggert, R. Sengpiel, Y. Wang, N. Wierckx, L. M. Blank, A. Spiess, W. Leitner, C. Bolm, M. Wessling, A. Jupke, M. Rosenbaum, J. Büchs, *Biotechnol. Biofuels* **2018**, *11*, 279.

[8] For selected reviews for C–H functionalization, see: a) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245; b) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788; c) C. Sambiagio, D. David Schöbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603; d) M. Gulías, J. L. Mascareñas, *Angew. Chem.* **2016**, *128*, 11164; *Angew. Chem., Int. Ed.* **2016**, *55*, 11000; e) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107; f) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; g) J. Ye, M. Lautens, *Nature Chem.* **2015**, *7*, 863; h) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc.* **2014**, *87*, 751; i) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; j) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; k) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; l) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; m) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; n) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.

[9] T. Satoh, M. Miura, in: *Science of Synthesis, Catalytic Transformations via C-H Activation 1* (Vol. Ed.; J.-Q. Yu), Thieme, Stuttgart, **2016**, *2015/3a*, pp 197-228.

[10] For recent examples, see: a) R. Yoshimoto, Y. Usuki, T. Satoh, *Chem. Lett.* **2019**, *48*, 461; b) T. Morita, H. Morisaka, T. Satoh, M. Miura, *Asian J. Org. Chem.* **2018**, *7*, 1330; T. Okada, A. Sakai, T. Hinoue, T. Satoh, Y. Hayashi, S. Kawauchi, K. Chandrababunaidu, M. Miura, *J. Org. Chem.* **2018**, *83*, 5639; T. Morita, T. Satoh, M. Miura, *Org. Lett.* **2017**, *19*, 1800.

[11] R. Yoshimoto, H. Morisaka, Y. Usuki, Y. Shibata, K. Tanaka, T. Satoh, *Chem. Lett.* **2020**, *49*, 1481.

[12] Tanaka and Shibata reported the first example for dehydrogenative coupling using $[Cp^ERhCl_2]_2$ catalyst: a) Y. Shibata, K. Tanaka, *Angew. Chem.* **2011**, *123*, 11109; *Angew. Chem., Int. Ed.* **2011**, *50*, 10917. See also their recent paper: Y. Nagashima, S. Ishigaki, J. Tanaka, K. Tanaka, *ACS Catal.* **2021**, *11*, 13591.

[13] For Cp*Rh-catalyzed dehydrogenative alkenylation of benzamides, see: a) F. Wang, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5430; b) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096; *Angew. Chem., Int. Ed.* **2011**, *50*, 1064; c) T. Besset, N. Kuhl, F. W. Patureau, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7167.

[14] The β-hydrogen elimination step proceeded regioselectively, probably due to the formation of resonance stabilized products.

[15] For Cp*Rh-catalyzed dehydrogenative alkenylation of acetanilides, see: F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982.

[16] For Cp*Rh-catalyzed dehydrogenative alkenylation of benzoic acids, see: a) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 3024; b) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407.

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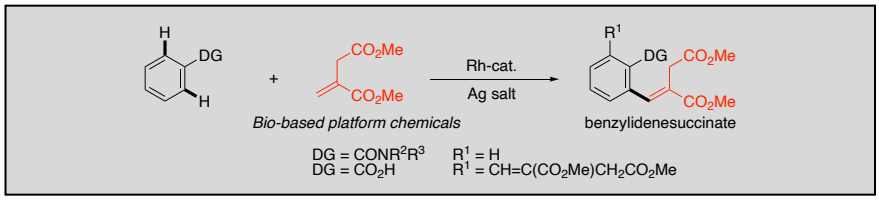

Benzylidenesuccinates can be readily synthesized through the rhodium(III)-catalyzed dehydrogenative coupling aromatic amides and carboxylic acids with dimethyl itaconate. Itaconic acid and its derivatives are recognized as promising building-blocks due to their ready availability and renewability.