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Ruthenium-Catalyzed Cross-Coupling of Maleimides with Alkenes

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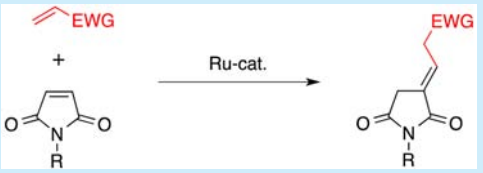
Supporting Information

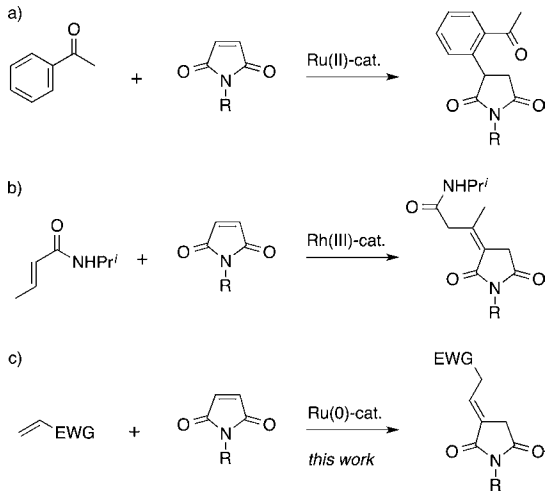
ABSTRACT: The cross-coupling of maleimides with electron-deficient alkenes such as acrylates proceeds smoothly under ruthenium catalysis. This unique C−C coupling provides a simple, straightforward synthetic method for preparing alkylidene succinimide derivatives.



Since maleimide derivatives are stable and readily available building blocks, they are of importance in polymer manufacturing. Maleimide structures are also recognized as synthetically important units because of their high reactivities toward various reactions, including Diels−Alder reactions and Michael additions. One of the important applications is for the modification of proteins by attaching maleimide derivatives via nucleophilic addition of the thiol moiety of cysteine residues to maleimides.[1] This is a key step in preparing chemically modified human hemoglobin such as maleimide−poly(ethylene glycol)-modified hemoglobin (MP4).[2a] A thiol addition to an alkylated maleimide was used in the multistep synthesis of Cdc25 phosphatase inhibitors.[2b] As these examples show, nucleophilic additions to maleimides provide simple synthetic routes toward variously substituted succinimide derivatives. Such succinimide frameworks are often seen in pharmaceuticals and biologically active natural products.[3] Compared with well-developed coupling reactions with nucleophiles, the direct C−C coupling with electronically neutral or deficient reagents has been less explored.[4]

On the other hand, transition-metal-catalyzed direct cross-coupling reactions between readily available substrates have been developed to provide efficient synthetic routes.[5] A representative example is the Ru(0)-catalyzed direct coupling of simple aromatic ketones such as acetophenone with alkenes to form the corresponding *ortho*-alkylated ketones.[6] Recently, the relevant Ru(II)-catalyzed coupling of aromatic ketones with maleimides was disclosed to produce 3-arylsuccinimides (Scheme 1a).[7] Very recently, Kim and co-workers reported the Rh(III)-catalyzed direct coupling of acrylamides with maleimides through amide-directed C−H bond cleavage (Scheme 1b).[8] In the context of our studies on ruthenium-catalyzed direct coupling reactions,[6,9] we have found that *N*-substituted maleimides smoothly undergo intermolecular cross-coupling with other electron-deficient alkenes such as acrylates (Scheme 1c). Notably, the cross-coupling between these

Scheme 1. Cross-Coupling with Maleimides



electron-deficient alkenes took place exclusively, with no homocoupling product being detected. Some deuterium-labeling experiments have been conducted to obtain mechanistic information. These new findings are described herein.

In an initial attempt, *N*-cyclohexylmaleimide (**1a**) (0.5 mmol) was treated with butyl acrylate (**2a**) (1 mmol) in the presence of $RuH_2(CO)(PPh_3)_3$ (0.025 mmol, 5 mol %) under N_2 in toluene at 120 °C for 5 h, and the corresponding coupling product, butyl (*E*)-3-(1-cyclohexyl-2,5-dioxopyrrolidin-3-ylidene)propanoate (**3aa**), was obtained in 87% yield (Table 1, entry 1). In previously reported Ru(0)-catalyzed reactions, $RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$ showed higher activity than $RuH_2(CO)(PPh_3)_3$.[10] In the present reaction, the use of

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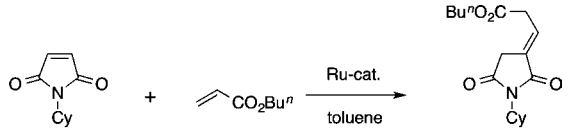
Table 1. Reaction of *N*-Cyclohexylmaleimide (1a) with Butyl Acrylate (2a)[a]



1a 2a 3aa

entry	Ru-cat.	temp (°C)	yield (%)[b]
1	$RuH_2(CO)(PPh_3)_3$	120	87
2	$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$	120	93
3[c]	$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$	120	85
4	$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$	135	92
5	$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$	110	70
6[d]	$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$	120	84

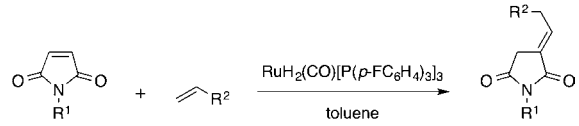
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), and Ru-cat. (0.025 mmol) under N_2 in toluene (3 mL) for 5 h, unless otherwise noted. [b]Isolated yields based on the amount of **1a** used. [c]In PhCl (3 mL). [d]**1a** (5.6 mmol), **2a** (11.2 mmol), and Ru-cat. (0.28 mmol) were employed.

$RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$ gave a somewhat better result (entry 2). In PhCl, the yield of **3aa** slightly decreased (entry 3). While increasing the reaction temperature to 135 °C did not show any influence, decreasing it to 110 °C retarded the reaction (entries 4 and 5). It should be noted that the gram-scale synthesis of **3aa** could be achieved by a simple scale-up. Thus, treatment of **1a** (5.6 mmol) with **2a** (11.2 mmol) in the presence of $RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$ (0.28 mmol) gave **3aa** (1.45 g) in 84% yield (entry 6).

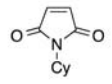
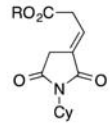
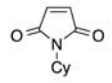
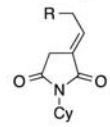
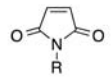
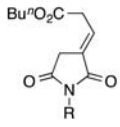
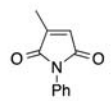
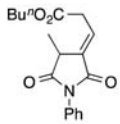
With the optimized conditions in hand (Table 1, entry 2), the cross-coupling of various maleimides **1a–i** with electron-deficient alkenes **2b–h** was next examined (Table 2). A series of acrylates **2b–f** coupled with **1a** smoothly to afford the corresponding products **3ab–af** in 81–94% yield (entries 1–5). Although *N*,*N*-dimethylacrylamide (**2g**) also underwent the coupling (entry 6), the reaction with acrylonitrile (**2h**) did not proceed at all (entry 7).[11] *N*-Alkyl- and *N*-arylmaleimides **1b–h** reacted with **2a** to give **3ba–ha** in fair to good yields (entries 8–14). In contrast to these *N*-substituted maleimides, *N*-unsubstituted maleimide itself did not react with **2a** at all. An *N*- and 3-substituted maleimide, *N*-cyclohexyl-3-methyl-1*H*-pyrrole-2,5-dione (**1i**), coupled with **2a** in a similar manner to afford **3ia** (entry 15). The C–C coupling seems to take place at the less hindered 4-position of **1i**.

To obtain some mechanistic information, coupling reactions using deuterated substrates were examined (Scheme 2). The reaction of **1g** with deuterated butyl acrylate (CD_2=$CDCO_2Bu$, **2a**-d_3, 80% D at the vinylic positions of the acrylate moiety) was conducted under the standard conditions, and the resulting mixture was post-treated by silica gel column chromatography to isolate **3ga**-d_2 in 62% yield (Scheme 2a). It was confirmed that the deuterium at the α-position of the butoxycarbonyl moiety was completely exchanged with proton during the post-treatment. At the β-position, D/H exchange during the reaction took place to somewhat reduce the D content. Instead, deuterium was introduced at the sp^3 carbon of the succinimide ring (39% D for the methylene). Meanwhile, the reaction of deuterated *N*-phenylmaleimide (**1g**-d_2, 40% D at the vinylic positions of the maleimide moiety) with unlabeled **2a** gave **3ga**-d_2 in 56% yield (Scheme 2b). After the reaction, the D content at the sp^3 carbon of the succinimide ring became 12% (for the methylene), accompanied by simultaneous deuterium incorporation at the β-position of the butoxycarbonyl moiety.

Table 2. Reaction of Maleimides 1 with Alkenes 2[a]

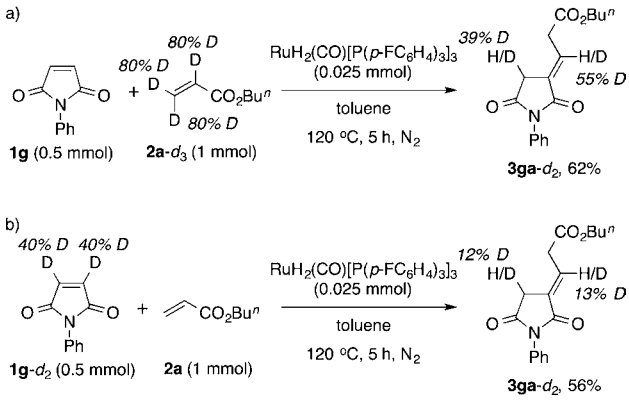


1 2 3

entry	1	2	product	yield (%)[b]
1	 1a	 2b: R = Bu^i	 3ab: R = Bu^i	81
2		2c: R = Bu^t	3ac: R = Bu^t	94
3		2d: R = Me	3ad: R = Me	84
4		2e: R = Et	3ae: R = Et	90
5		2f: R = Cy	3af: R = Cy	85
6	 1a	 2g: R = $CONMe_2$	 3ag: R = $CONMe_2$	47
7		2h: R = CN	3ah: R = CN	0
8	 1b: R = Me	 2a	 3ba: R = Me	85
9	1c: R = Bu^t		3ca: R = Bu^t	83
10	1d: R = $C_{12}H_{25}$		3da: R = $C_{12}H_{25}$	60
11	1e: R = $C_{18}H_{37}$		3ea: R = $C_{18}H_{37}$	78
12	1f: R = Bn		3fa: R = Bn	83
13	1g: R = Ph		3ga: R = Ph	67
14	1h: R = *o*-BrC_6H_4		3ha: R = *o*-BrC_6H_4	83
15	 1i	2a	 3ia	35

[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), and $RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$ (0.025 mmol) under N_2 in toluene (3 mL) for 5 h at 120 °C. [b]Isolated yields based on the amount of **1** used.

Scheme 2. Reactions of Deuterium-Labeled Substrates



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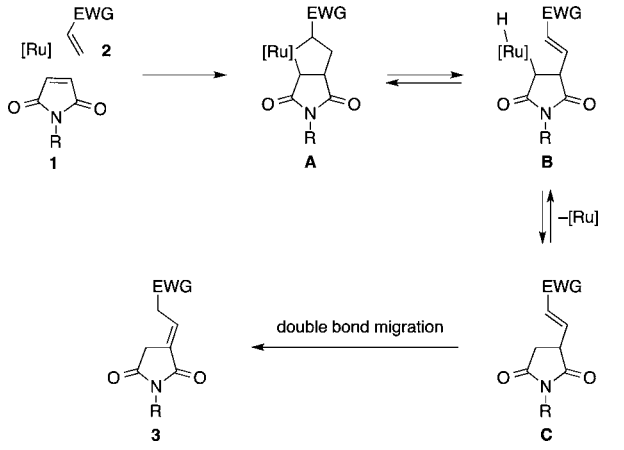
On the basis of these results and literature information,[12−14] one plausible mechanism for the direct coupling of **1** with **2** is illustrated in Scheme 3. Oxidative cyclization of **1** and **2** with a

Scheme 3. Plausible Mechanism for the Reaction of 1 with 2



ruthenium(0) species generated in the reaction medium gives five-membered ruthenacycle intermediate **A**.[13] Then β-hydrogen elimination and reductive elimination take place via **B** to form **C**. Thus, deuterium incorporation at the sp^3 carbon of the succinimide ring in the reaction of **1g** with deuterated butyl acrylate **2a**-d_3 (Scheme 2a) can occur at this step. Intermediate **C** undergoes double-bond migration[8] to produce **3**. The observed deuterium incorporation at the β-position of the butoxycarbonyl moiety in Scheme 2b implies that the β-hydrogen elimination step to go from **A** to **B** and the reductive elimination step to go from **B** to **C** are reversible. Besides the oxidative cyclization mechanism, however, the participation of another pathway initiated by the addition of a hydridoruthenium species across the double bonds cannot be excluded completely.[14]

In summary, we have demonstrated that maleimides readily undergo cross-coupling with electron-deficient alkenes under ruthenium catalysis. A variety of alkylidene succinimide derivatives could be prepared selectively. Work is underway toward the further development of the catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02244.

Experimental procedures and characterization data of products (PDF)

Crystallographic data for **3aa** (CIF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For example, see: Svergun, D. I.; Ekström, F.; Vandegriff, K. D.; Malavalli, A.; Baker, D. A.; Nilsson, C.; Winslow, R. M. *Biophys. J.* **2008**, *94*, 173.

(2) (a) Goertz, O.; Kirschner, M. H.; Lilienfein, H.; Babilas, P.; Steinau, H. U.; Andree, C.; Daigeler, A.; Stachon, A.; Homann, H.; Langer, S. *Eur. J. Med.Res.* **2009**, *14*, 123. (b) Brault, L.; Denancé, M.; Banaszak, E.; El Maadidi, S.; Battaglia, E.; Bagrel, D.; Samadi, M. *Eur. J. Med. Chem.* **2007**, *42*, 243.

(3) For example, see: (a) Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc.* **1987**, *109*, 4409. (b) Kornet, M. J.; Crider, A. M.; Magarian, E. O. *J. Med. Chem.* **1977**, *20*, 405.

(4) For recent examples, see: (a) Yang, Z.-H.; Chen, Z.-H.; An, Y.-L.; Zhao, S.-Y. *RSC Adv.* **2016**, *6*, 23438. (b) An, Y.-L.; Yang, Z.-H.; Zhang, H.-H.; Zhao, S.-Y. *Org. Lett.* **2016**, *18*, 152. (c) Moon, Y.; Jeong, Y.; Kook, D.; Hong, S. *Org. Biomol. Chem.* **2015**, *13*, 3918.

(5) For selected recent reviews of direct coupling involving C−H functionalization, see: (a) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (b) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (c) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751. (d) Jin, T.; Zhao, J.; Asao, N.; Yamamoto, Y. *Chem. - Eur. J.* **2014**, *20*, 3554. (e) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (f) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419. (g) Bonin, H.; Sauthier, M.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 645. (h) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927. (i) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (j) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (k) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (l) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092. (m) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (n) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (o) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (p) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (q) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (r) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (s) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (t) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (u) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (v) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (w) Satoh, T.; Miura, M. *Synthesis* **2010**, *2010*, 3395. (x) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (y) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (z) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(6) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. For reviews, see: (b) Kakiuchi, F.; Kochi, T.; Murai, S. *Synlett* **2014**, *25*, 2390. (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *2008*, 3013. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (f) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62.

(7) (a) Bettadapur, K. R.; Lanke, V.; Prabhu, K. R. *Org. Lett.* **2015**, *17*, 4658. (b) Lanke, V.; Bettadapur, K. R.; Prabhu, K. R. *Org. Lett.* **2015**, *17*, 4662.

(8) Sharma, S.; Han, S. H.; Oh, Y.; Mishra, N. K.; Lee, S. H.; Oh, J. S.; Kim, I. S. *Org. Lett.* **2016**, *18*, 2568.

(9) (a) Okada, T.; Nobushige, K.; Satoh, T.; Miura, M. *Org. Lett.* **2016**, *18*, 1150. (b) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.;

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Org. Lett. 2016, 18, 4598−4601

Miura, M. *Adv. Synth. Catal.* **2014**, *356*, 1521. (c) Itoh, M.; Hashimoto, Y.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 8098. (d) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 3990. (e) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *J. Org. Chem.* **2013**, *78*, 638. (f) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058. (g) Hashimoto, Y.; Ortloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett.* **2012**, *41*, 151. (h) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165. (i) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706.

(10) (a) Mitsudo, T.-a.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492. (b) Tokoro, Y.; Sugita, K.; Fukuzawa, S.-i. *Chem. - Eur. J.* **2015**, *21*, 13229.

(11) It is possible that relatively strong coordination of **2h** disturbed the desired cross-coupling. Actually, the addition of **2h** (1 mmol) to the reaction of **1a** with **2a** under the standard conditions (Table 1, entry 2) decreased the yield of **3aa** to 65%.

(12) Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, *27*, 893.

(13) (a) Hiroi, Y.; Komine, N.; Komiya, S.; Hirano, M. *Organometallics* **2014**, *33*, 6604. (b) Hirano, M.; Sakate, Y.; Komine, N.; Komiya, S.; Bennett, M. A. *Organometallics* **2009**, *28*, 4902.

(14) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160.

DOI: 10.1021/acs.orglett.6b02244
Org. Lett. 2016, 18, 4598−4601