Ruthenium-Catalyzed Cascade C-H Functionalization of Phenylacetophenones

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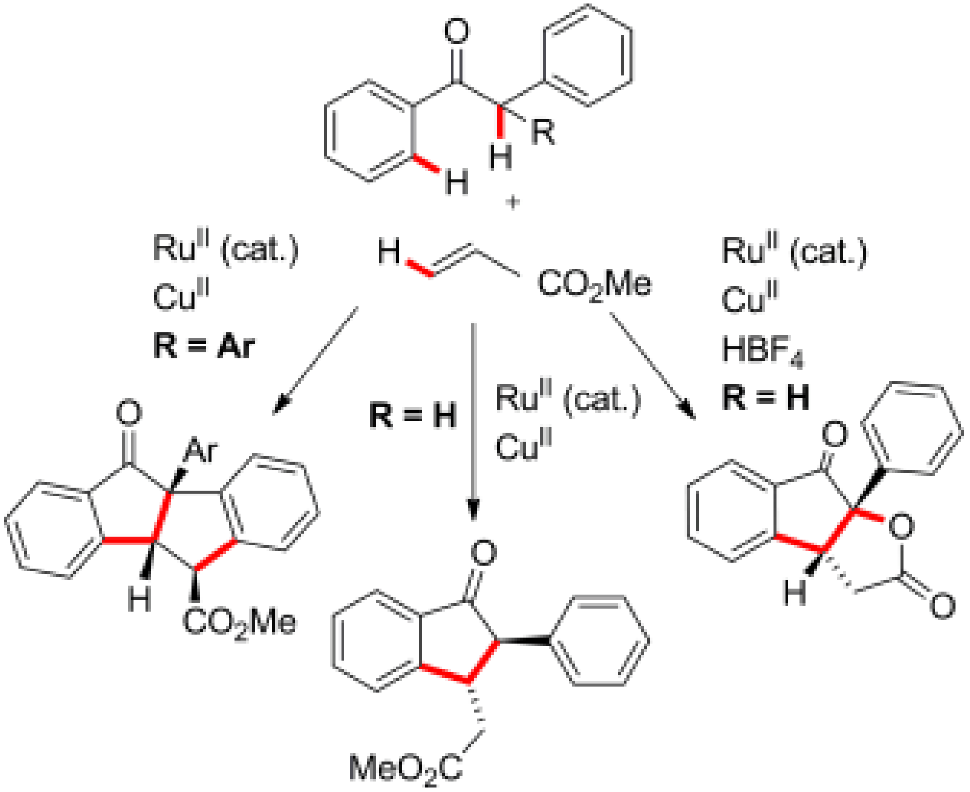

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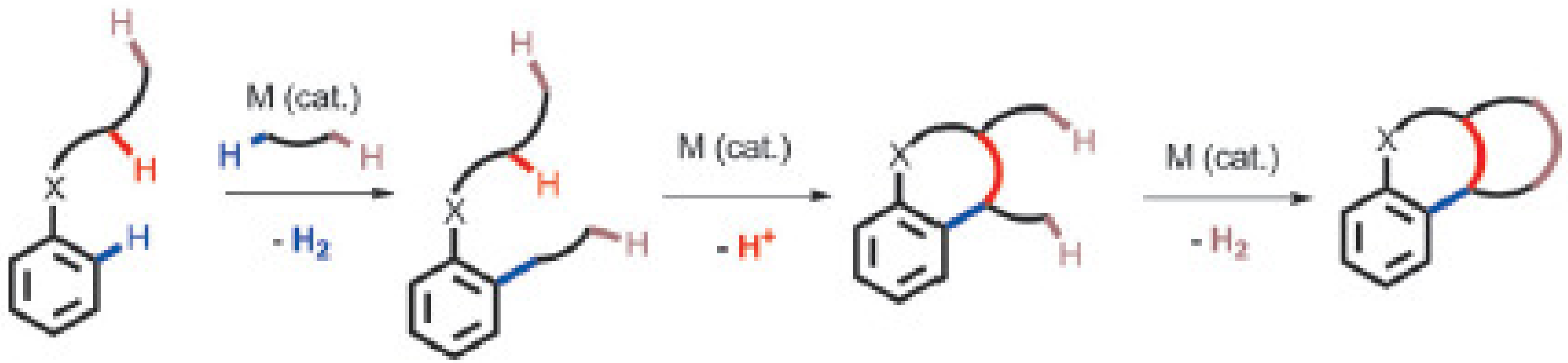
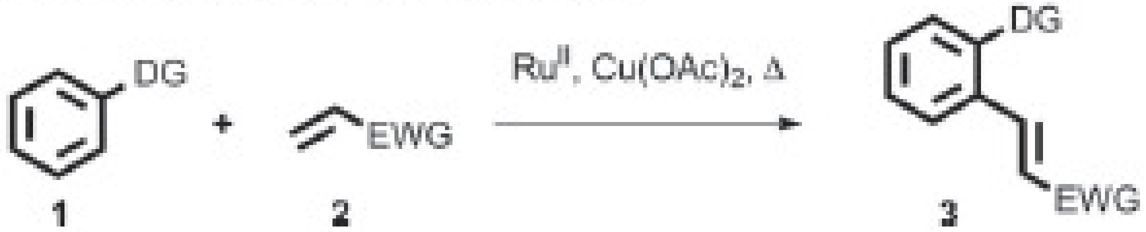
Metal-catalyzed cascade C–H functionalization



Ruthenium-catalyzed C–H alkenylation



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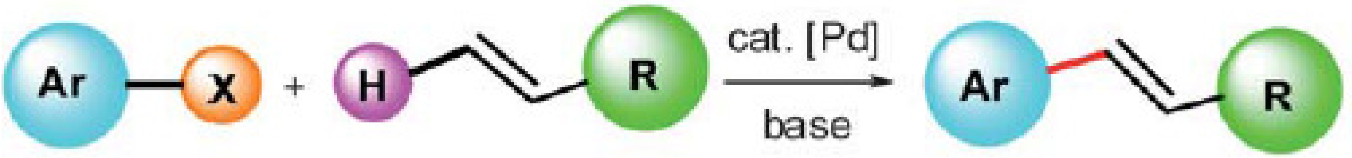
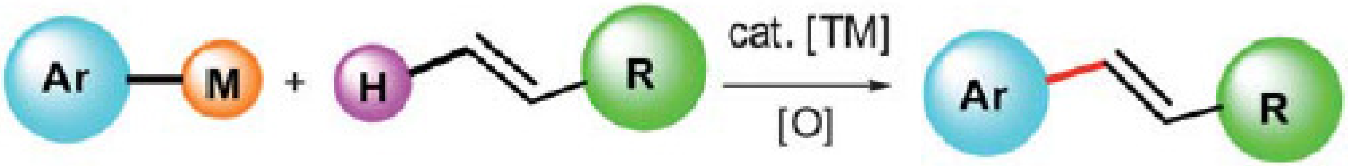
Strategies for styrene synthesis via alkenylations of arenes

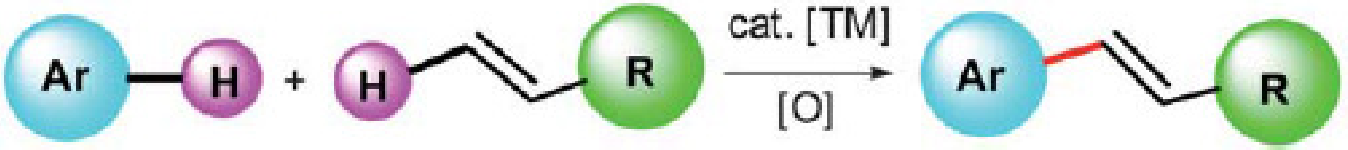
(a) Mizoroki-Heck reaction



(b) Alkenylation via transmetallation



(c) C–H/C–H bond functionalization



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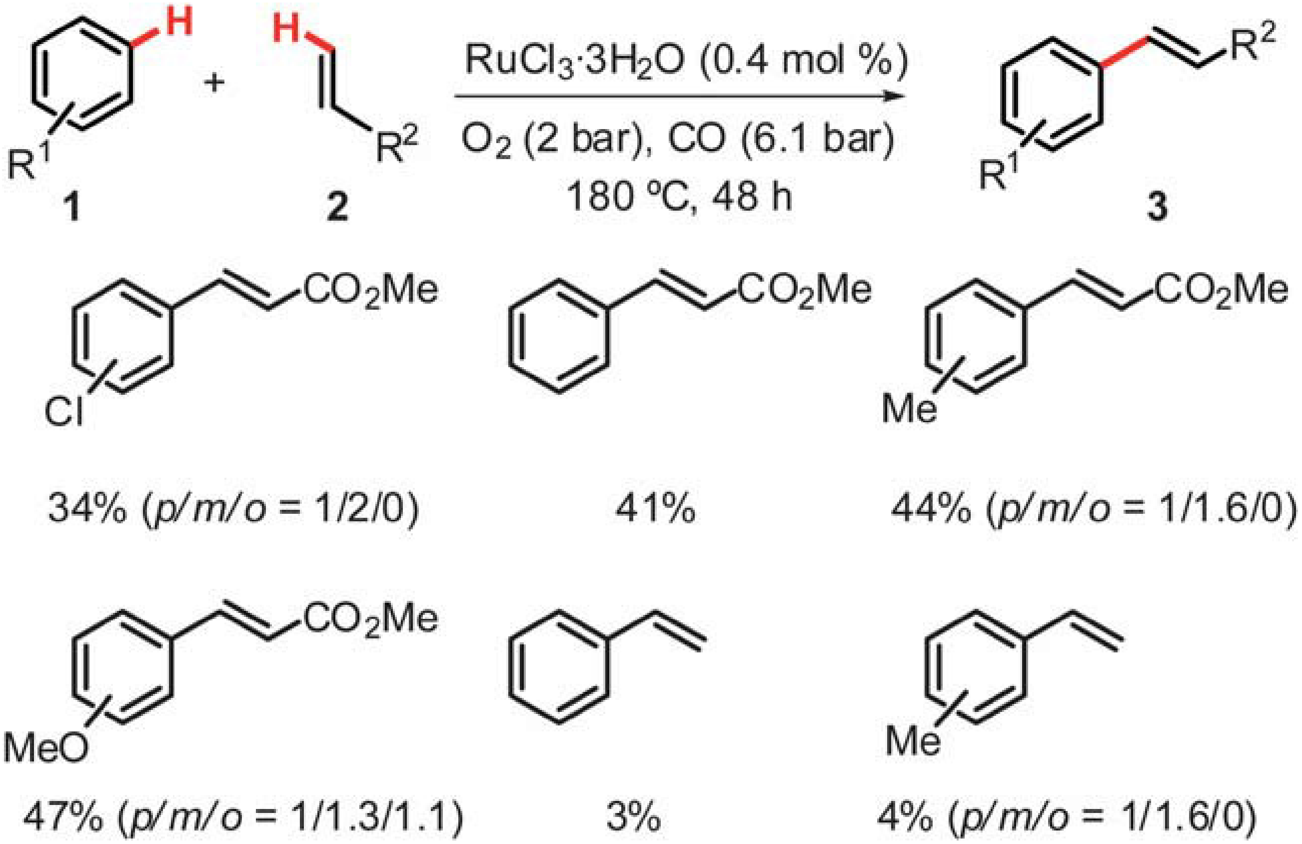
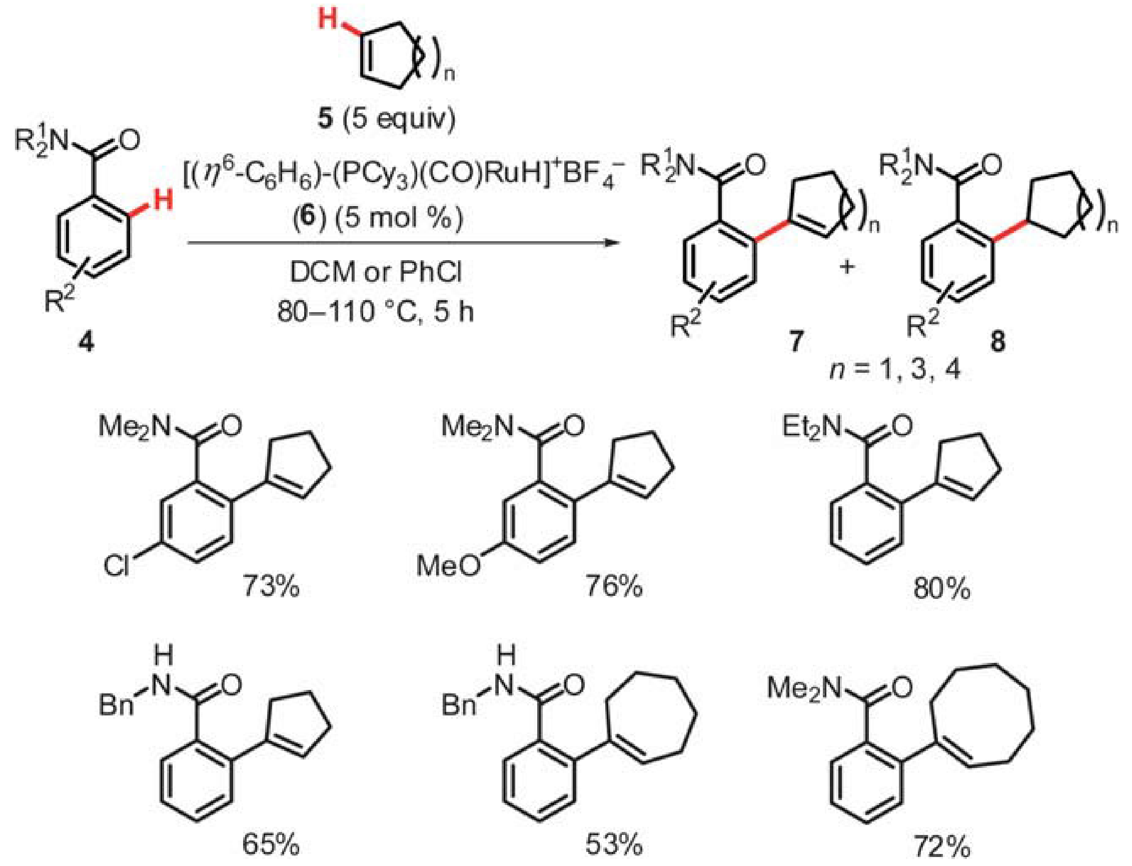
Ruthenium-catalyzed direct alkenylations of simple arenes



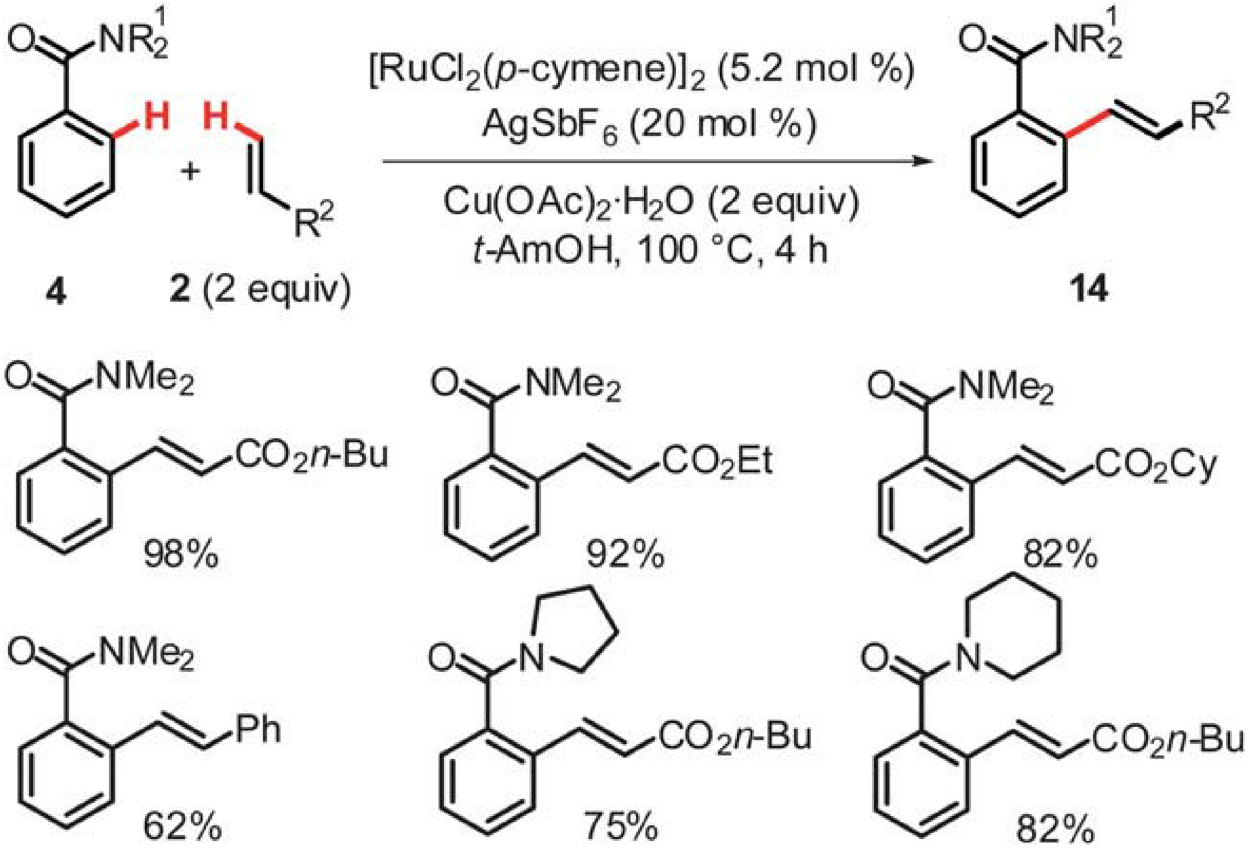
H. Weissman, X. Song, D. Milstein *J. Am. Chem. Soc.* **2001**, *123*, 337–338
Adopted from S. I. Kozhushkov, L. Ackermann *Chem. Sci.* **2013**, *4*, 886–896

Ruthenium-catalyzed alkenylations of benzamides **4** with unactivated alkenes **5**



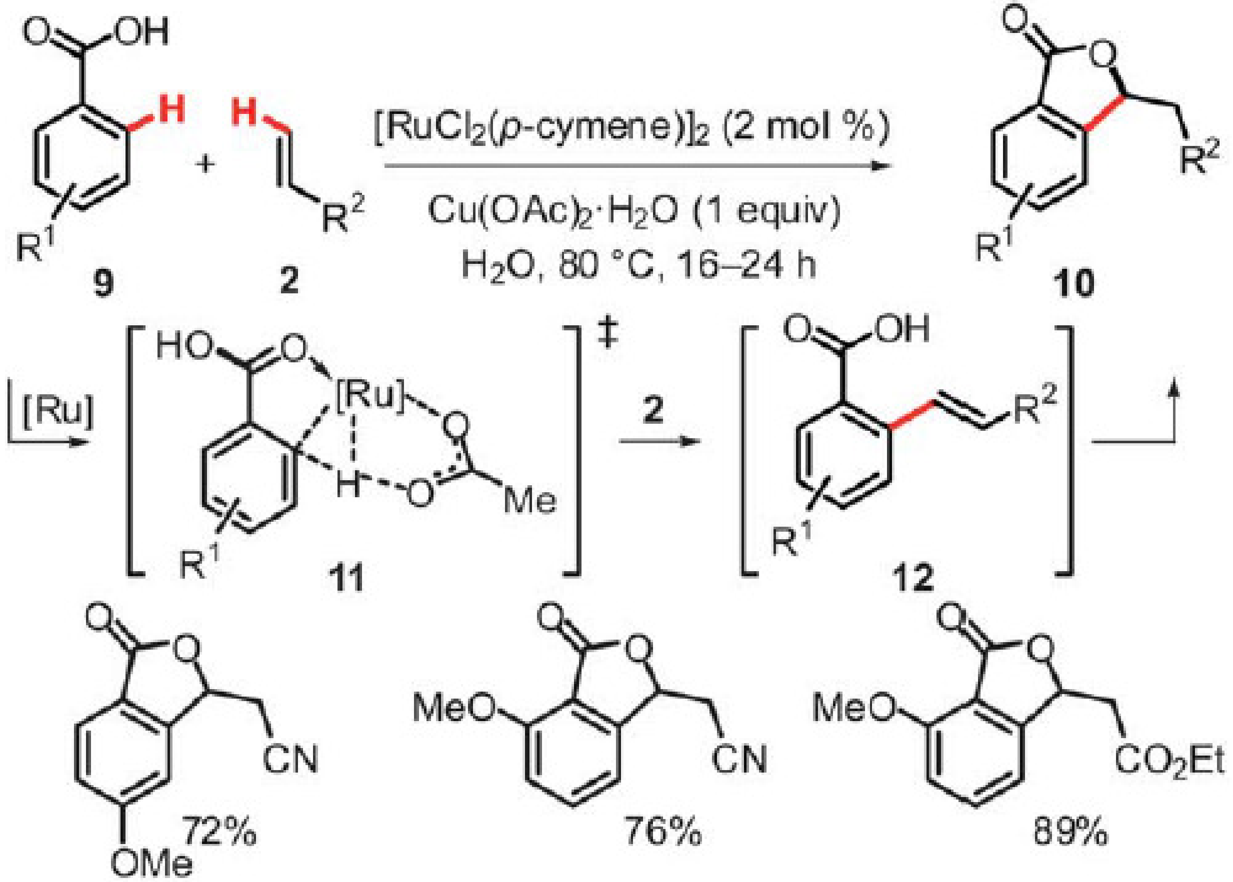
K.-H. Kwon, D. W. Lee, C. S. Yi *Organometallics* **2010**, *29*, 5748–5750
Adopted from S. I. Kozhushkov, L. Ackermann *Chem. Sci.* **2013**, *4*, 886–896

Ruthenium-catalyzed alkenylations of benzamides **4** with activated alkenes **2**



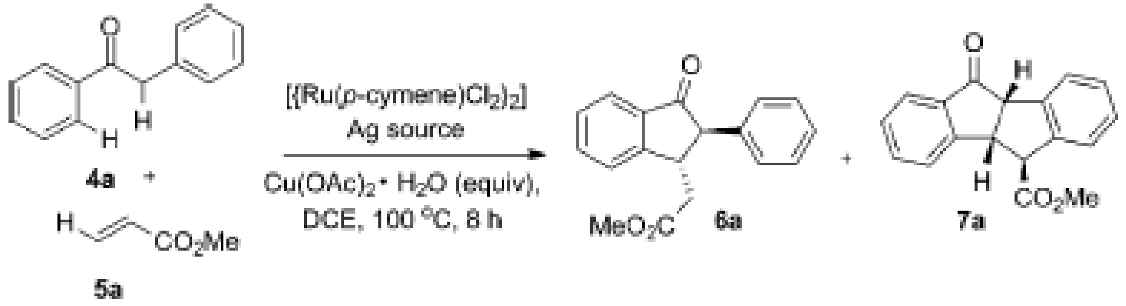
Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura *Chem. Lett.* **2012**, *41*, 151–153
Adopted from S. I. Kozhushkov, L. Ackermann *Chem. Sci.* **2013**, *4*, 886–896

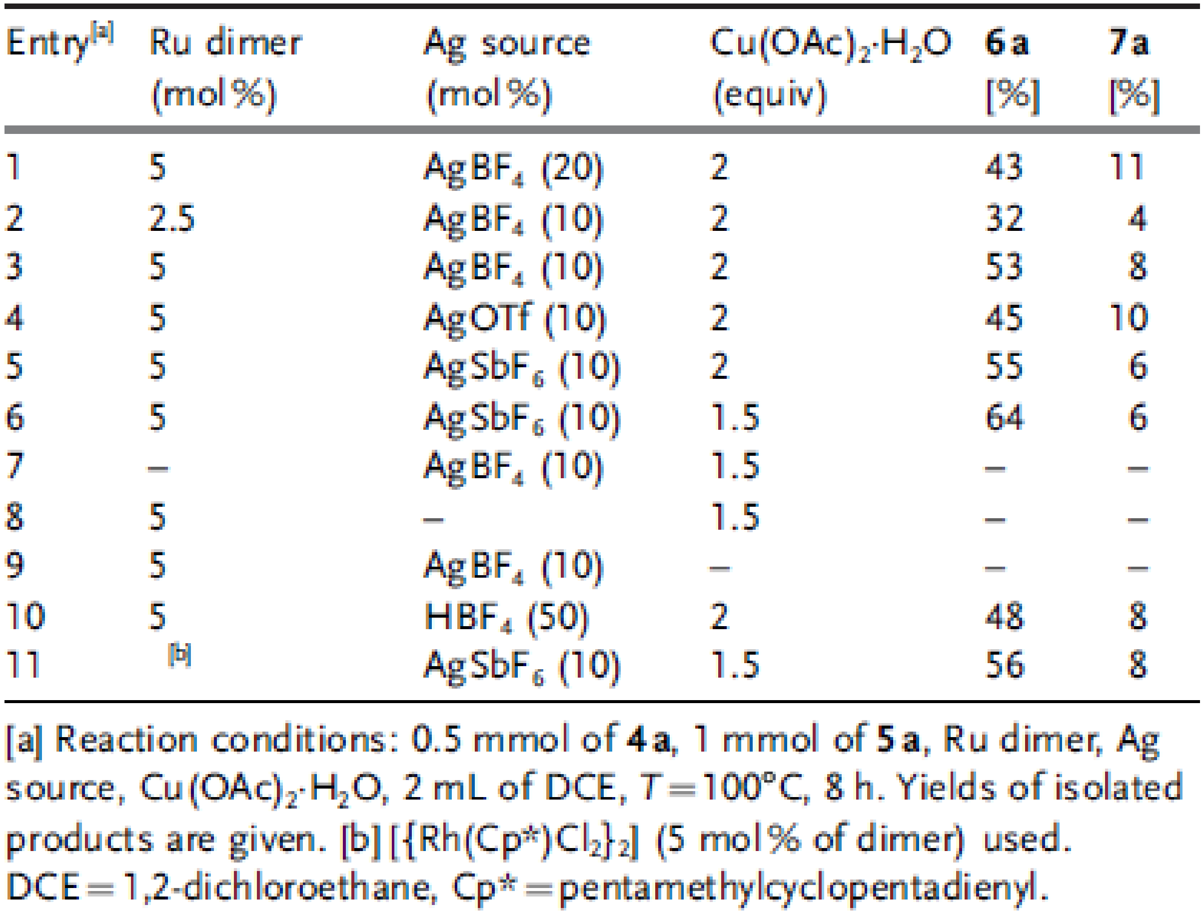
Ruthenium-catalyzed alkenylation-oxa-Michael sequence with benzoic acids **9**



L. Ackermann, J. Pospech *Org. Lett.* **2011**, *13*, 4153–4155
Adopted from S. I. Kozhushkov, L. Ackermann *Chem. Sci.* **2013**, *4*, 886–896

Table 1: Reaction development.

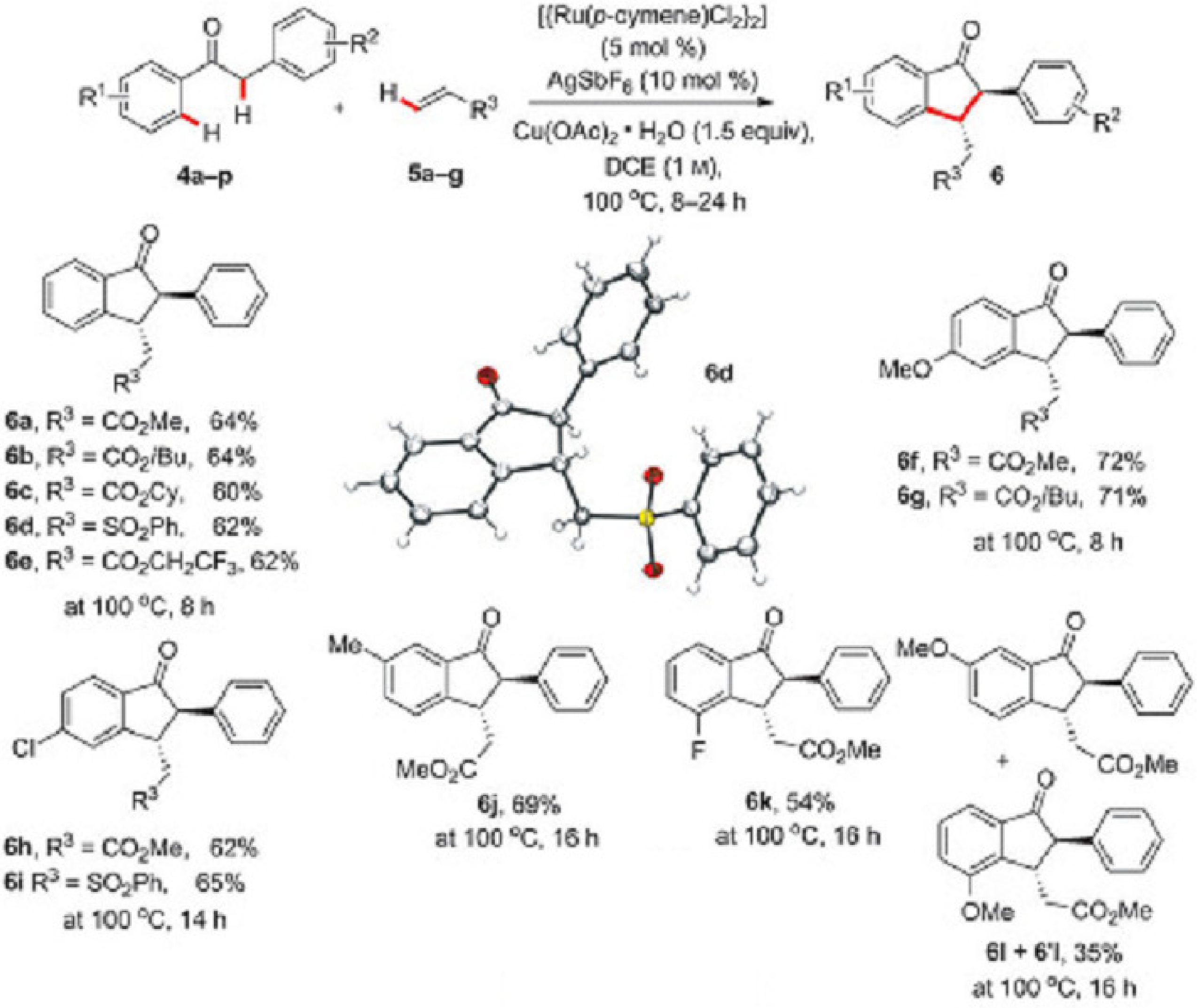




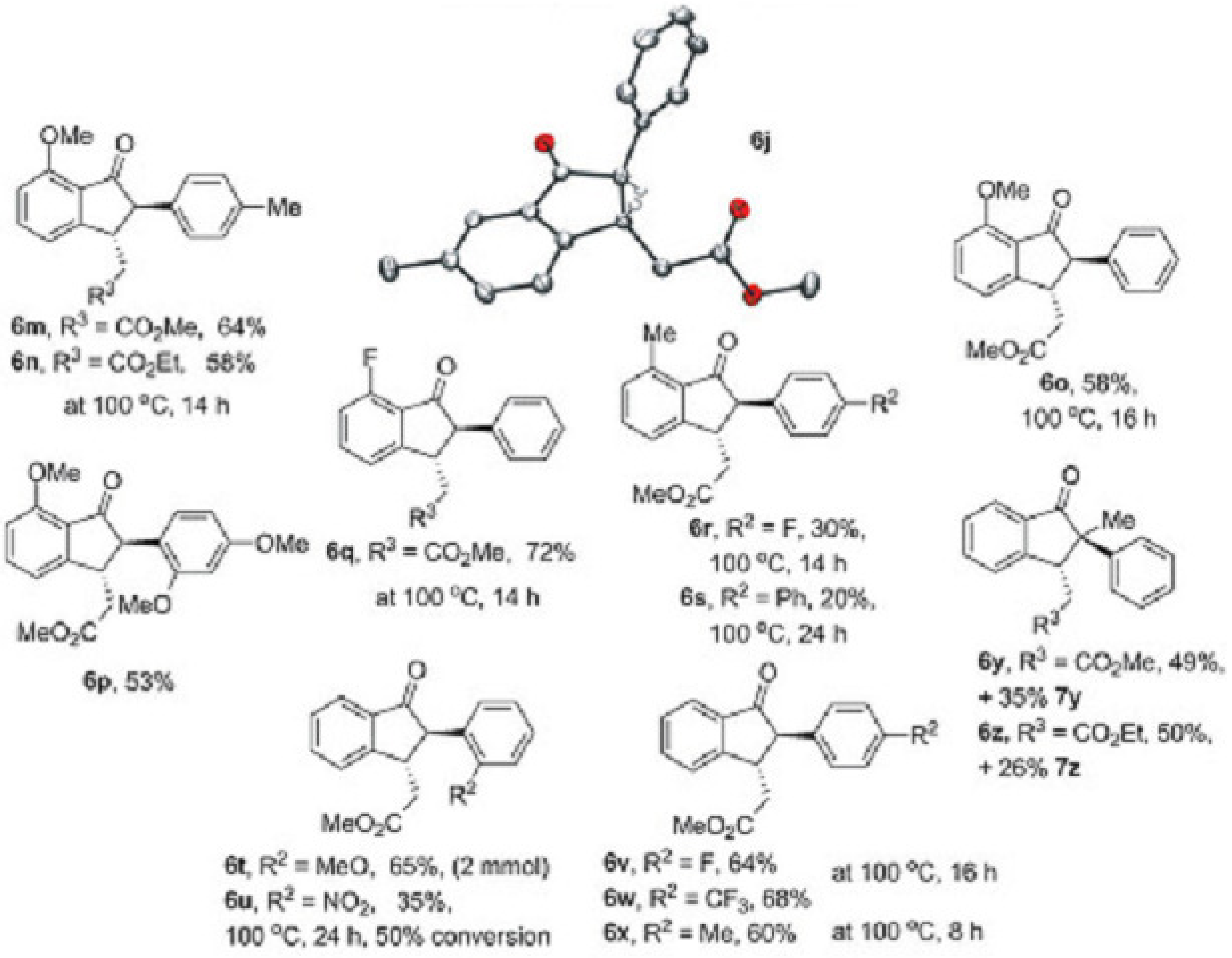
Entry[a]	Ru dimer (mol %)	Ag source (mol %)	$Cu(OAc)_2 \cdot H_2O$ (equiv)	**6a** [%]	**7a** [%]
1	5	$AgBF_4$ (20)	2	43	11
2	2.5	$AgBF_4$ (10)	2	32	4
3	5	$AgBF_4$ (10)	2	53	8
4	5	AgOTf (10)	2	45	10
5	5	$AgSbF_6$ (10)	2	55	6
6	5	$AgSbF_6$ (10)	1.5	64	6
7	–	$AgBF_4$ (10)	1.5	–	–
8	5	–	1.5	–	–
9	5	$AgBF_4$ (10)	–	–	–
10	5	HBF_4 (50)	2	48	8
11	[b]	$AgSbF_6$ (10)	1.5	56	8

[a] Reaction conditions: 0.5 mmol of **4a**, 1 mmol of **5a**, Ru dimer, Ag source, $Cu(OAc)_2 \cdot H_2O$, 2 mL of DCE, $T = 100°C$, 8 h. Yields of isolated products are given. [b] $[\{Rh(Cp^*)Cl_2\}_2]$ (5 mol% of dimer) used. DCE = 1,2-dichloroethane, Cp* = pentamethylcyclopentadienyl.

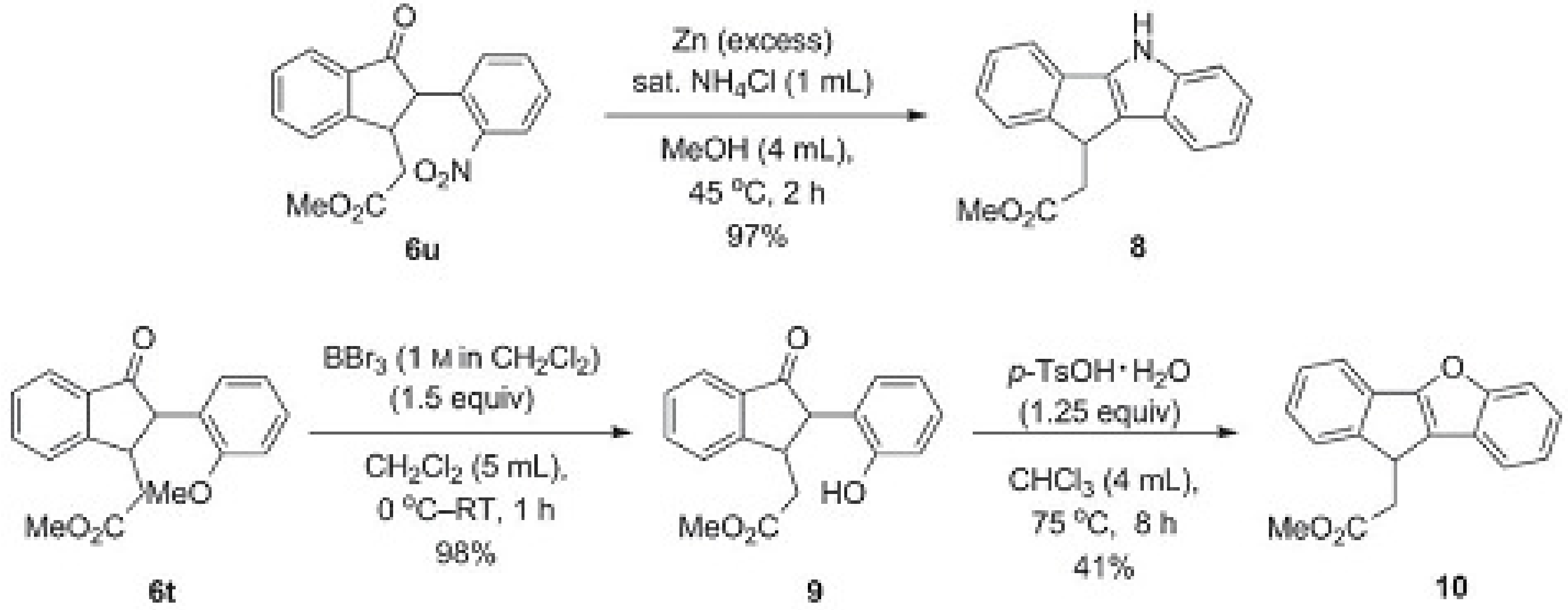
1-Indanone substrate scope



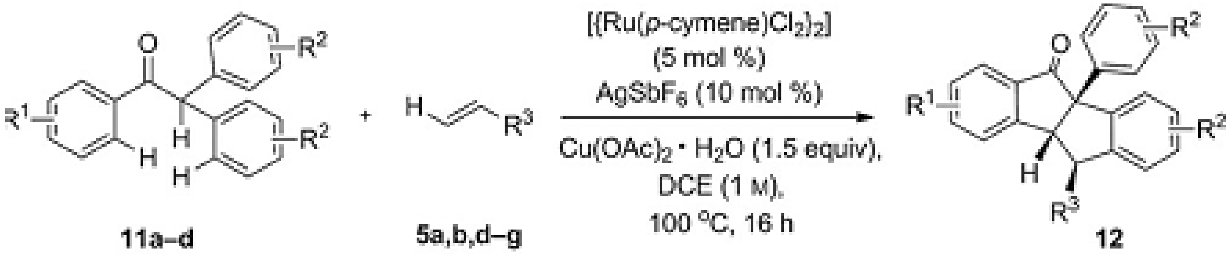
1-Indanone substrate scope (continued)

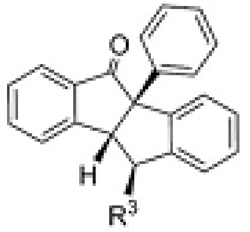


1-Indanone post-transformations

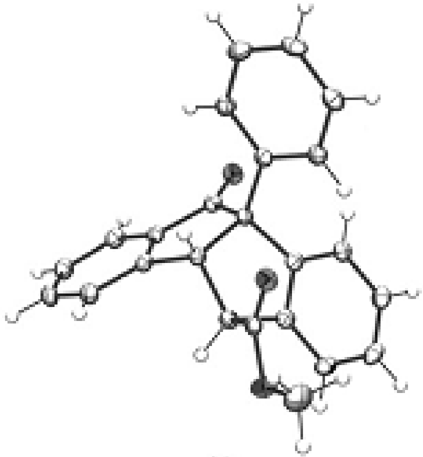


Indeno indene substrate scope

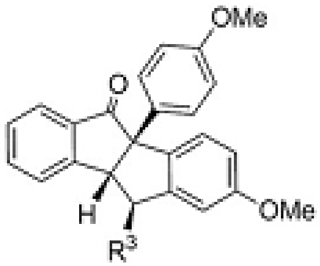




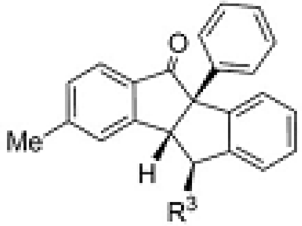
12a, R^3 = CO$_2$Me, 89%
12b, R^3 = CO$_2$Et, 77%
12c, R^3 = CO$_2$*i*Bu, 70%
12d, R^3 = CO$_2$Cy, 75%
12e, R^3 = SO$_2$Ph, 93%
12f, R^3 = CO$_2$CH$_2$CF$_3$, 81%



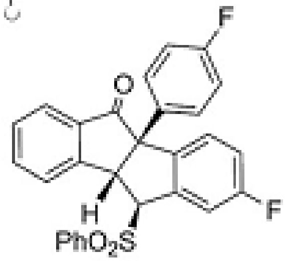
12a



12g, R^3 = CO$_2$Me, 85%
12h, R^3 = CO$_2$*n*Bu, 75%

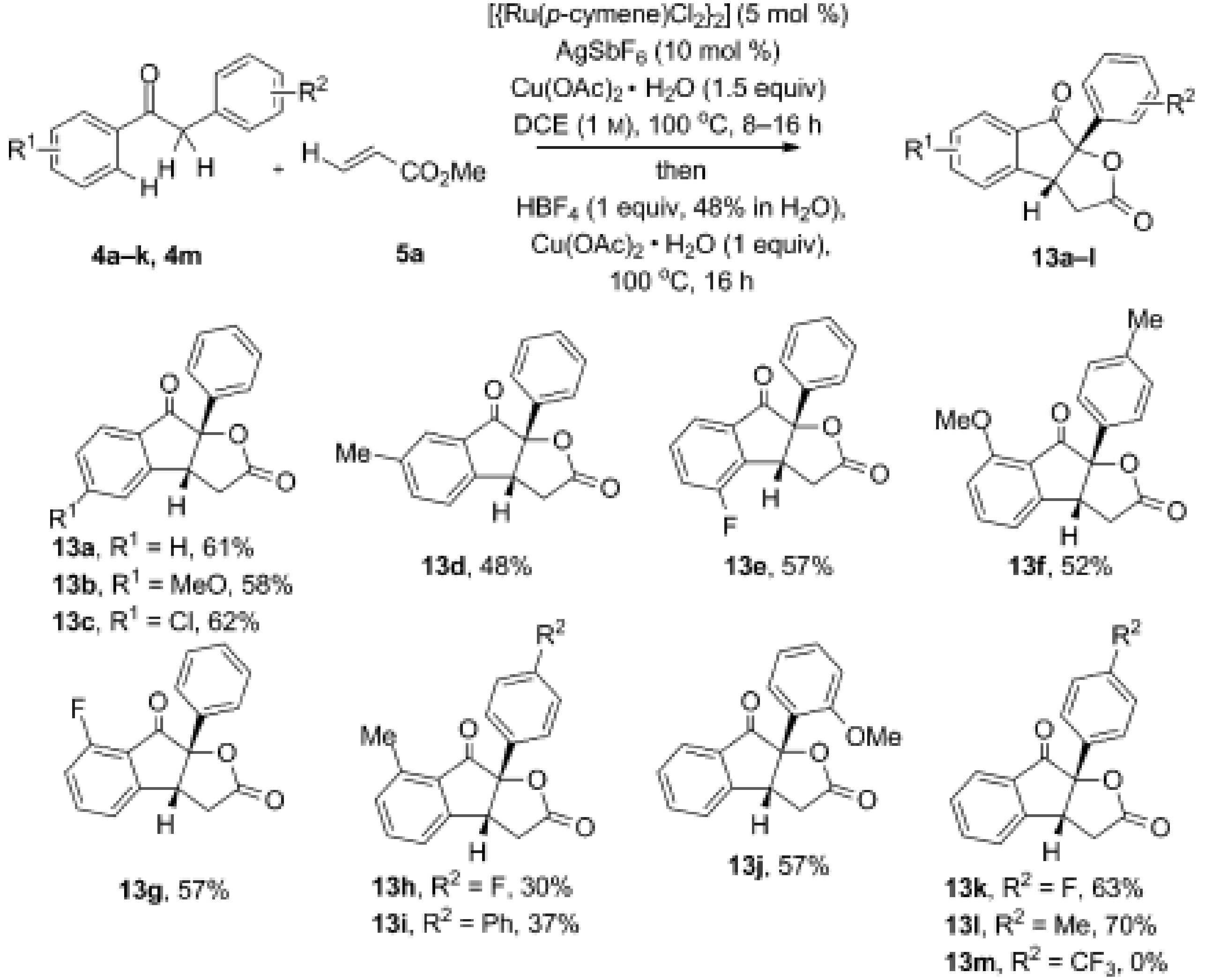


12i, R^3 = CO$_2$Me, 92%
12j, R^3 = SO$_2$Ph, 93%

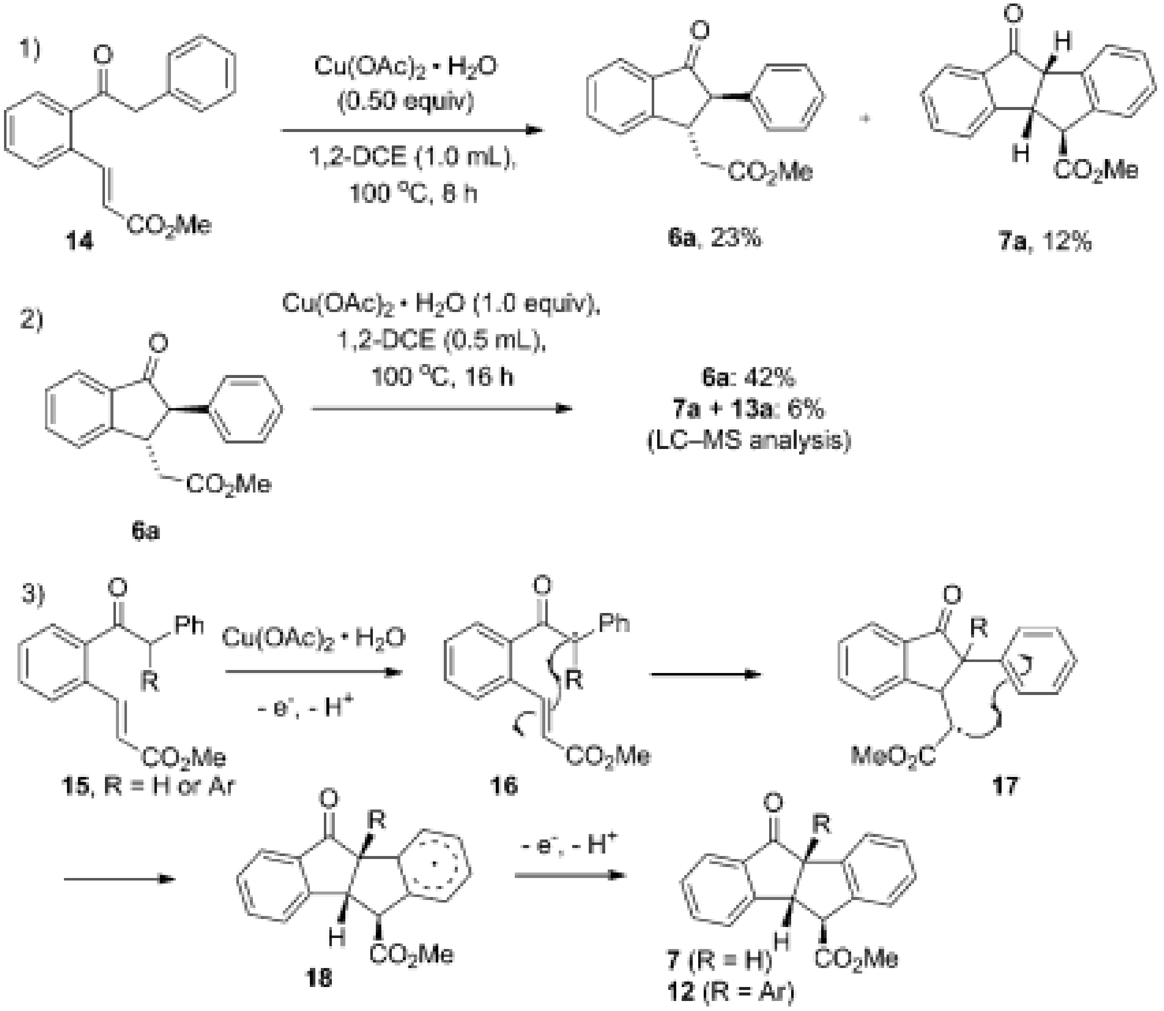


12k, 83%

Substrate scope for alkenylation–cyclization–lactonization



Mechanistic investigations and possible reaction pathway



CONCLUSIONS

- Ruthenium(II)-catalyzed cascade C-H functionalization process that can be directed three different ways according to the choice of substrate and reaction conditions was developed and studied.
- Possible further directions:
  - Additional mechanistic and substrate scope studies (acrylonitrile, heterocycles)
  - Asymmetric version