Published in final edited form as:
J Am Chem Soc. 2013 April 10; 135(14): 5364–5367. doi:10.1021/ja402274g.

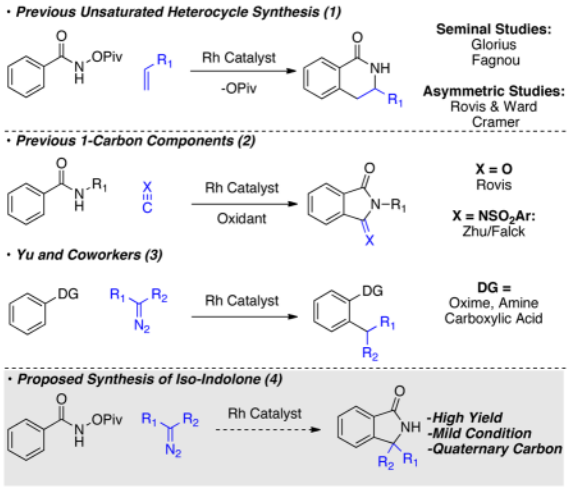
A Coupling of Benzamides and Donor/Acceptor Diazo–Compounds to form γ-Lactams via Rh(III)–Catalyzed C–H Activation

Todd K. Hyster, **Kyle E. Ruhl**, and **Tomislav Rovis***
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Abstract

The coupling of *O*-pivaloyl benzhydroxamic acids with donor/acceptor diazo compounds provides iso-indolones in high yield. The reaction tolerates a broad range of benzhydroxamic acids and diazo compounds including substituted 2,2,2-trifluorodiazo ethanes. Mechanistic experiments suggest that C–H activation is turnover limiting and irreversible, while insertion of the diazo compound favors electron deficient substrates.

Multicomponent reactions catalyzed by transition metals represent a powerful approach for the synthesis of heterocycles.[1] This concept has been extensively explored in the Rh(III) catalyzed synthesis of nitrogen containing heterocycles mediated by C–H activation.[2] A wide swath of unsaturated heterocycles can be accessed though coupling amides, amines, oximes, and anilines with alkynes to access isoquinolones,[3] pyridones,[3d,4] isoquinolines,[5] pyridines,[5g,6] indoles,[7] and pyrroles.[7b,8]



The ability to access nitrogen containing hetero-cycles bearing stereogenic carbons is important due to their prevalence in medicinal targets and natural products.[9,10] Recently,

Corresponding Author: rovis@lamar.colostate.edu.
Present Addresses
Department of Chemistry, Colorado State University, Fort Collins, CO 80526

ASSOCIATED CONTENT
Detailed experimental procedures, characterization, and mechanistic data. This material is available free of charge via the Internet at http://pubs.acs.org

Glorius[11] and Fagnou[3e] demonstrated that alkenes can be used to access partially saturated nitrogen containing heterocycles (eq 1). In the presence of an enzyme or chiral cyclopentadiene ligand this reaction can be rendered asymmetric.[12] Currently absent from this family of reactivity is the ability to access γ-lactams with the potential to control stereochemistry in the process. The key to achieving this reactivity is identification of a suitable 1-carbon component.

Examples of 1-carbon components in Rh(III) C–H activation reactions are rare. Previously, we found amides could be coupled with carbon monoxide to provide a range of phthalimides in good yield (eq 2).[13] Concurrent work by Zhu and Falck found isocyanides to be competent coupling partners in an analogous reaction.[14] Carbon monoxide and isocyanides function as 1-carbon components because the carbon has carbenic character. Elegant work by Yu took advantage of the carbenic character of electron deficient diazo-compounds to *ortho*-functionalize a variety of directing group containing arenes (eq 3).[15] Given the importance of γ-lactams, we were interested in using diazo-compounds as 1-carbon components in a cyclization reaction that would provide iso-indolones (eq 4).

We believed a significant barrier to this reactivity would be the need to inhibit protonation of the metal-lacycle. The report by Yu suggests protonation of the rhodacycle occurs rapidly when mono-dentate directing groups are used.[15] Fagnou[3e] and Glorius[11] found that use of a bi-dentate directing group precludes β-hydride elimination in the synthesis of dihydroisoquiolones. We imagined that this type of directing group would also be effective toward inhibiting unwanted protonation events. In a set of initial experiments, we chose to explore donor/acceptor diazo-compounds because they are less prone to dimerization while providing interesting products with a stereogenic carbon.

Initial coupling of amide **1a** with diazo-ester **2a** using super-stoichiometric CsOPiv in MeOH gave the desired product in 24% yield with the remainder of the mass balance being methanolysis of the pivalate ester in the starting material (Table 1, entry 1). A screen of solvents revealed CH_3CN to be ideal, providing lactam **3a** in 78% yield (Table 1, entry 4). Replacing CsOPiv with CsOAc gave comparable yields (Table 1, entry 5). We were pleased to find that a sub-stoichiometric amount of base did not have a detrimental effect on yield (Table 1, entry 6). Finally, modification of the concentration allowed the desired lactam to be isolated in 81% yield after 150 minutes. The catalyst loading can be decreased to 0.4 mol % when the reaction is performed on gram scale (Table 1, Entry 8). The use of O-methyl hydroxamic acid in place of **1a** delivers only 10% yield of the protonated product, but none of the desired product.

The ideal conditions in hand, the scope of iso-indolone formation was tested with differentially substituted benzhydroxamic acids (Table 2). The reaction affords the desired product with a variety of electronically different *para*-substituted amides in high yield (Table 2, **3a–3f**). Substitution at the *meta*-position plays an important role in controlling the regioselectivity of the C–H activation event. When *meta*-methyl benzhydroxamic acid is used (Table 2, 3h), C–H activation occurs exclusively *para*- to the methyl group presumably to avoid sterically disfavored interactions. However, when a methoxy group is placed at the *meta*-position (Table 2, 3g), a 1.1:1 ratio of regioisomers is observed. This effect is also observed with naphthyl-amides (Table 2, 3i), where a 2:1 ratio of regioisomers is observed. By comparison, the less electron deficient tetrahydronaphthylene benzhydroxamic acid gives a single regioisomer (Table 2, 3j). Presumably this decrease in regioselectivity can be attributed to the increase in acidity of the *ortho* C–H bond. Increasing the kinetic acidity of the C–H bond overwhelms the steric bias of the C–H activation to give a mixture of products. The gallic acid derived amide and the heterocyclic substrate also fare well in the reaction, although increased reaction temperatures are required (Table 2, 3k–l).

We moved to explore the scope of diazo-compounds (Table 3). Acceptor diazo-compounds[16] dimerize rapidly under the reaction conditions, while acceptor/acceptor diazo compounds are almost completely unreactive, with less than 5% yield observed under these reactions conditions. Donor/acceptor diazo-compounds are broadly tolerated with reasonable scope. Differential substitution on the ester gave the desired product in high yield (Table 3, **4a–b**). Cyclic diazo substrates deliver the desired spiro-compounds in high yield under the reaction conditions (Table 3, **4c–d**). A wide range of substituents can be tolerated on the aromatic ring.[17] While electron poor substrates provide the desired product rapidly under the standard reaction conditions (Table 3, **4e, 4j, 4i**), electron rich substrates are far more sluggish and require elevated temperatures and prolonged reaction times (Table 3, 4f, 4h). We were pleased to find that heteroaryl diazo esters also provide product, albeit in lower yield (Table 3, **4k–l**). Elevated temperatures allowed for acceptor diazo esters to be incorporated in good yield (Table 3, **e3**).

While screening electron-withdrawing groups on the donor/acceptor diazo compound, we found that amides and phosphonates provide product in very low yield. In contrast, we were pleased to find the 1-phenyl, 2,2,2-trifluoro diazoethane, as described by Davies and coworkers,[18] delivered the desired product in high yield (Chart 1, **5a**). Electron deficient aromatic groups on these trifluoroethyl diazo substrates function well in the reaction with high yield and rapid reaction times (Chart 1, **5b**, **5d–f**). As observed previously, electron rich aromatic groups provide products in substantially lower yield even at high temperatures (Chart 1, **5c**). These products contain quaternary carbons with a trifluoromethyl group, a substitution pattern not easily accessed using other methods.[19]

A series of mechanistic experiments were performed to elucidate the nuances of the reaction (Scheme 1). Competition experiments were used to determine the electronic preference of the reaction. When *para*-bromo benzamide **1c** was run in competition with the unsubstituted amide **1a** the reaction favors the electron deficient amide in a 1.9:1 ratio (Scheme 1a). This experiment suggest that C–H activation favors more acid C–H bonds. Indeed, initial rate kinetic isotope studies revealed a KIE value of 2.6 (Scheme 1b). Together these studies suggest that C–H activation occurs via a concerted-metallation deprotonation (CMD) mechanism, and the C–H activation does not proceed through a Wheland intermediate.[20] These experiments are consistent with the observation that reactions involving substrates bearing more electron donating groups are sluggish.

The reversibility of the C–H activation can be determined by removing the diazo compound and running the reaction in the presence of d_3-MeCN (Scheme 1c). After 15 minutes less than 1% deuterium incorporation is observed at the *ortho*-positions, as determined by ^{1}H NMR. After 150 minutes the degree of deuterium incorporation increases to 7%. These results suggest that C–H activation in largely irreversible over the time scale of the reaction, and is consistent with previous reports by Fagnou[3e] and Glorius.[21]

A competition experiment was used to determine the reactions preference for electronically different donor/acceptor diazo compounds (Scheme 1d). When *para*-bromophenyl methyl diazo acetate **2e** is run in competition with **2a**, the electron deficient substrate is favored 1.6:1 after 15 minutes. These results suggest that migratory insertion or reductive elimination favors the more electron deficient substrate. Since reductive elimination should favor a more electron rich substrate, it is reasonable to surmise that migratory insertion favors an electron deficient diazo substrate because of its increased electrophilicity.

In conclusion, we have developed a new approach to access iso-indolones bearing a tetra-substituted carbon. A wide range of substrates are tolerated, including 1-aryl-2,2,2-

trifluoroethyldiazo compounds. Mechanistic studies reveal the reaction to operate under a mechanism similar to that of the synthesis of dihydroisoquinolones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

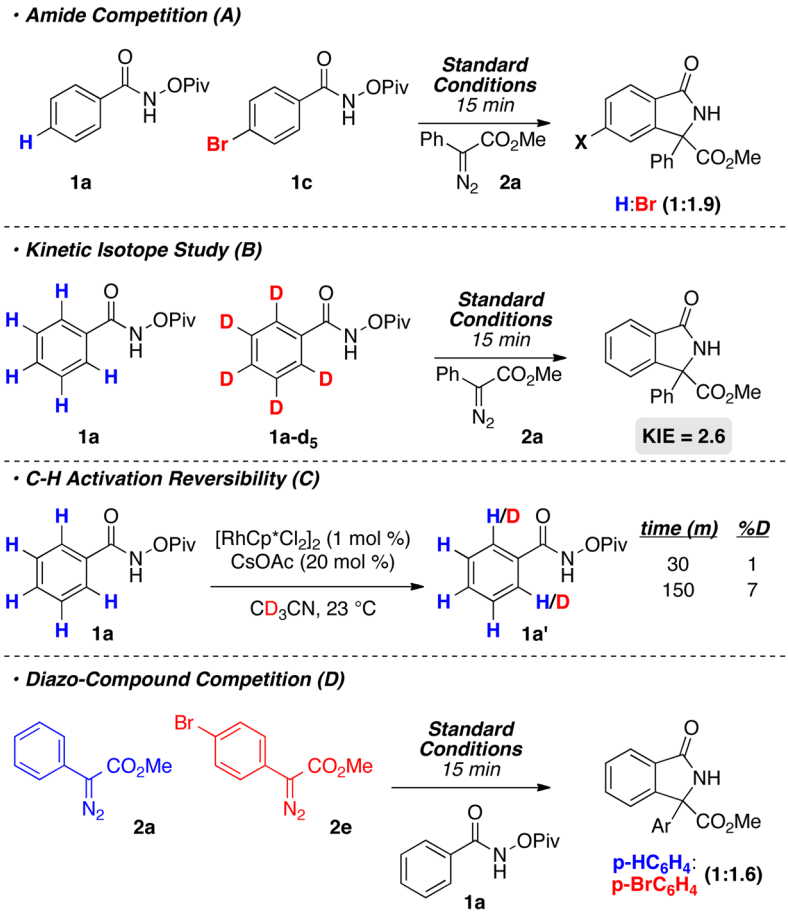
The authors declare no competing financial interest.

We thank NIGMS for generous support of this research (GM80442). T.R. thanks Amgen and Roche for unrestricted support and Johnson Matthey for a generous loan of Rh salts.

References

1. (a) D'Souza DM, Muller TJJ. Chem Soc Rev. 2007; 36:1095. [PubMed: 17576477] (b) Nakamura I, Yamamoto Y. Chem Rev. 2004; 104:2127. [PubMed: 15137788]
2. (a) Satoh T, Miura M. Chem Eur J. 2010; 16:11212. [PubMed: 20740508] (b) Zhu C, Wang R, Falck JR. Chem Asian J. 2012; 7:1502. [PubMed: 22492555] (c) Patureau FW, Wencel-Delord J, Glorius F. Aldrichemica Acta. 2012; 45:31.
3. (a) Guimond N, Gouliaras C, Fagnou K. J Am Chem Soc. 2010; 132:6909.(b) Mochida S, Umeda N, Hirano K, Satoh T, Miura M. Chem Lett. 2010; 39:744.(c) Hyster TK, Rovis T. J Am Chem Soc. 2010; 132:10565. [PubMed: 20662529] (d) Song G, Chen D, Pan CL, Crabtree RH, Li X. J Org Chem. 2010; 75:7487. [PubMed: 20923219] (e) Guimond N, Gorelsky SL, Fagnou K. J Am Chem Soc. 2011; 133:6449. [PubMed: 21452842] (f) Wang H, Grohmann C, Nimphius C, Glorius F. J Am Chem Soc. 2012; 134:19592. [PubMed: 23146122]
4. (a) Su Y, Zhao M, Han K, Song G, Li X. Org Lett. 2010; 12:5462. [PubMed: 21033749] (b) Hyster TK, Rovis T. Chem Sci. 2011; 2:1605.
5. (a) Guimond N, Fagnou K. J Am Chem Soc. 2009; 131:12050. [PubMed: 19705909] (b) Li L, Brennessel WW, Jones WD. J Am Chem Soc. 2008; 130:12414. [PubMed: 18714995] (c) Fukutani T, Umeda N, Hirano K, Satoh T, Miura M. Chem Commun. 2009; 34:5141.(d) Too PC, Wang YF, Chiba S. Org Lett. 2010; 12:5688. [PubMed: 21082771] (e) Morimoto K, Hirano K, Satoh T, Miura M. Chem Lett. 2011; 40:600.(f) Wang YF, Toh KK, Lee JY, Chiba S. Angew Chem Int Ed. 2011; 50:5927.(g) Hyster TK, Rovis T. Chem Commun. 2011; 47:11846.(h) Zhang X, Chen D, Zhao M, Jia A, Li X. Adv Synth Cat. 2011; 353:719.
6. Too PC, Noji T, Lim YJ, Li X, Chiba S. Synlett. 2011:2789.
7. (a) Stuart DR, Bertrand-Laperle M, Burgess KMN, Fagnou K. J Am Chem Soc. 2008; 130:16474. [PubMed: 19554684] (b) Stuart DR, Alsabeh P, Kuhn M, Fagnou K. J Am Chem Soc. 2010; 132:18326. [PubMed: 21133376] (c) Chen J, Song G, Pan CL, Li X. Org Lett. 2010; 12:5426. [PubMed: 21038875] (d) Huestis MP, Chan L, Stuart DR, Fagnou K. Angew Chem Int Ed. 2011; 50:1338.
8. Rakshit S, Patureau FW, Glorius F. J Am Chem Soc. 2010; 132:9585. [PubMed: 20578748]
9. McGrath NA, Brichacek M, Njardarson JT. J Chem Ed. 2010; 87:1348.
10. (a) Augner D, Gerbino DC, Slavov N, Neudorfl JM, Schmalz HG. Org Lett. 2011; 13:5374. [PubMed: 21902238] (b) Nozawa Y, Yamamoto K, Ito M, Sakai N, Mizoue K, Mizobe F, Hanada K. J Antibiot. 1997; 50:635. [PubMed: 9315074] (c) Comins D, Schilling S, Zhang Y. Org Lett. 2005; 7:95. [PubMed: 15624986] (d) Stuk TL, Assink BK, Bates RC, Erdman DT, Fedij V, Jennings SM, Lassig JA, Smith RJ, Smith TL. Org Process Res Dev. 2003; 7:851.(e) Belliotti TR, Brink WA, Kesten SR, Rubin JR, Wustrow DJ, Zoski KT, Whetzel SZ, Corbin AE, Pugsley TA, Heffner TG, Wise LD. Bioorg Med Chem Lett. 1998; 8:1499. [PubMed: 9873377]
11. Rakshit S, Grohmann C, Besset T, Glorius F. J Am Chem Soc. 2011; 133:2350. [PubMed: 21275421]

12. (a) Hyster TK, Knorr L, Ward TR, Rovis T. Science. 2012; 338:500. [PubMed: 23112327] (b) Ye B, Cramer N. Science. 2012; 338:504. [PubMed: 23112328]
13. Du Y, Hyster TK, Rovis T. Chem Commun. 2011; 47:12074.
14. Zhu C, Xie W, Falck JR. Chem Eur J. 2011; 17:12591. [PubMed: 21972033]
15. Chan WW, Lo SF, Zhao Z, Yu WY. J Am Chem Soc. 2012; 134:13565. [PubMed: 22860697]
16. Davies has defined diazo compounds as donor, acceptor or both; see: Morten D, Davies HML. Chem Soc Rev. 2011; 40:1857. [PubMed: 21359404]
17. Donor/acceptor diazo compounds bearing alkenes as the donor group underwent pyrazole formation; see: Manning JR, Davies HML. Org Synth. 2007; 84:334.
18. Denton JR, Sukumaran D, Davies HML. Org Lett. 2007; 9:2625. [PubMed: 17552531]
19. For select leading references, see: Guo Y, Zhao X, Zhang D, Murahashi S-i. Angew Chem Int Ed. 2009; 48:2047.Mizuta S, Galicia-Lopez O, Engle KM, Verhoog S, Wheel-house K, Rassias G, Gouverneur V. Chem Eur J. 2012; 18:8583. [PubMed: 22692972] Shibata N, Suzuki S, Furukawa T, Kawai H, Tokunaga E, Yuan Z, Cahard D. Adv Synth Cat. 2011; 353:2037.
20. (a) Lapointe D, Fagnou K. Chem Lett. 2010; 39:1118.(b) Wheland GW. J Am Chem Soc. 1942; 64:900.(c) Davies DL, Donald SMA, Al-Duaij O, Macgregor SA, Polleth M. J Am Chem Soc. 2006; 128:4210. [PubMed: 16568979]
21. Wang H, Glorius F. Angew Chem Int Ed. 2012; 51:7318.



Scheme 1.
Mechanistic Experiments

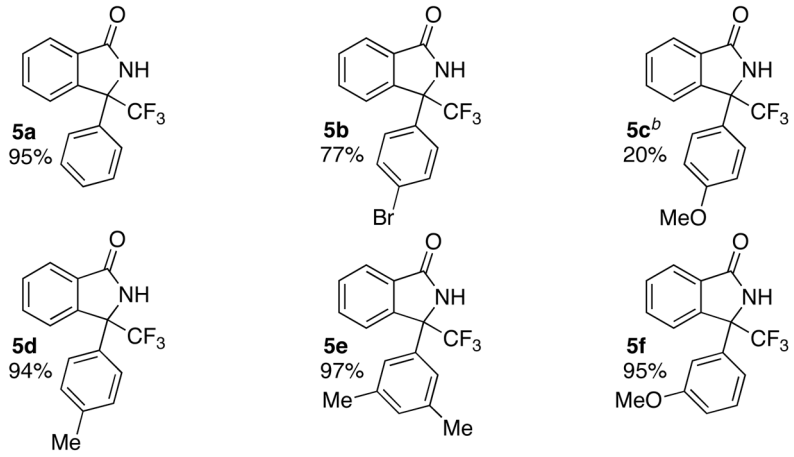
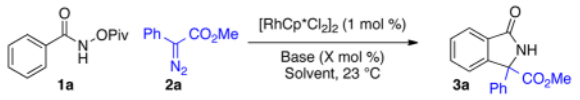


Chart 1.
Scope with 1-aryl 2,2,2-trifluoro diazoethanes
[a]For standard reaction conditions see Table 1. [b]Reaction conducted at 60 °C.

Table 1

Optimization of Reaction Conditions



1a 2a 3a

entry[a]	base	solvent	yield (%)[b]
1	CsOPiv (200 mol %)	MeOH (0.5 M)	24
2	CsOPiv (200 mol %)	EtOH (0.5 M)	33
3	CsOPiv (200 mol %)	TFE (0.5 M)	59
4	CsOPiv (200 mol %)	MeCN (0.5 M)	78
5	CsOAc (200 mol %)	MeCN (0.5 M)	80
6	CsOAc (20 mol %)	MeCN (0.1 M)	81[c]
7	-	MeCN (0.1 M)	0
8[d]	CsOAc (20 mol %)	MeCN (0.1 M)	75[c]

[a] Standard Conditions: **1a** (1 equiv), **2a** (1 equiv), $[RhCp^*Cl_2]_2$ (1 mol %).

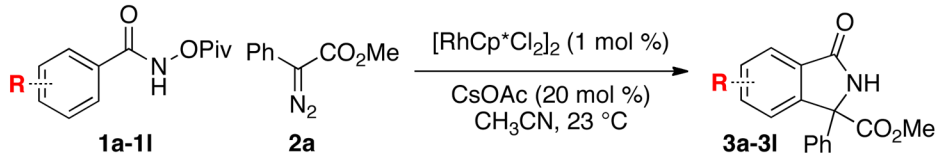
[b] Yield determined by HPLC.

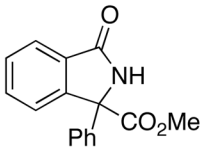
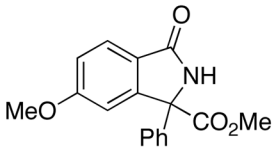
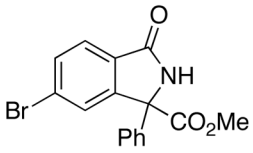
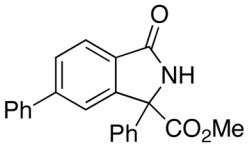
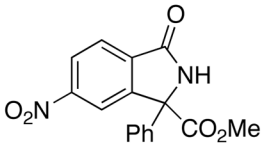
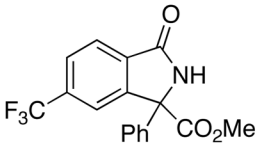
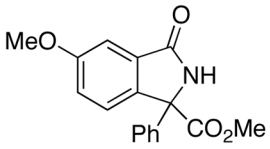
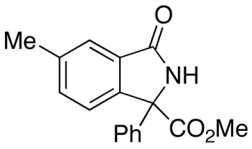
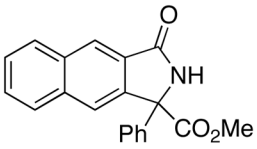
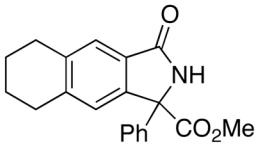
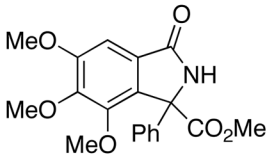
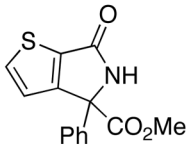
[c] Isolated Yield.

[d] Catalyst loading (0.4 mol %)

Table 2

Benzhydroxamic Acid Scope[a]



 **3a** 81 %	 **3b** 84 %	 **3c** 99 %
 **3d** 79%	 **3e** 88%	 **3f** 74 %
 **3g**[b,c] 74%	 **3h** 97%	 **3i**[d] 68 %
 **3j** 94%	 **3k**[c] 87%	 **3l**[c] 50 %

[a] For standard reaction conditions see Table 1.

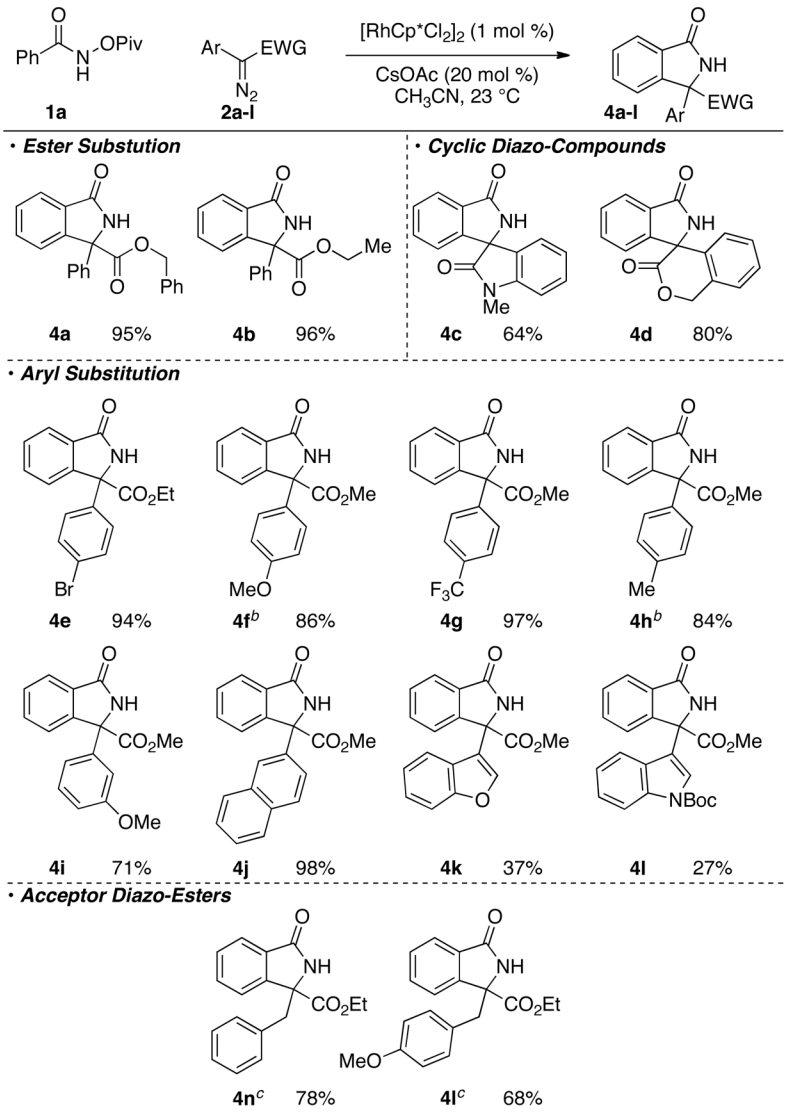
[b] Product isolated as a 1.1:1 ratio of regioisomers.

[c] Reaction conducted at 60 °C.

[d] Isolated as a 2:1 ratio of regioisomers.

Table 3

Scope of Donor/Acceptor Diazo Compounds[a]



[a]For standard reaction conditions see Table 1.

[b]Reaction conducted at 60 °C.

[c]Reactions conducted at 80 °C.