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Multicomponent Multicatalyst Reactions $(MC)^2R$: One-Pot Synthesis of 3,4-Dihydroquinolinones

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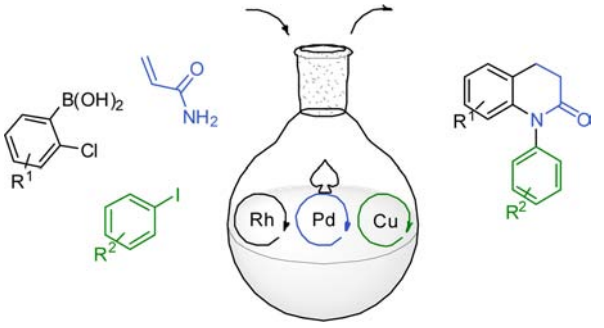
ABSTRACT



A Rh/Pd/Cu catalyst system led to an efficient synthesis of dihydroquinolinones in one-pot, two operations. The reaction features the first triple metal-catalyzed transformations in one reaction vessel, without any intermediate workup. The conjugate-addition/amidation/amidation reaction sequence is highly modular, divergent, and practical.

In addition to the development of new methods in synthetic organic chemistry, efficiency remains a major objective. Ultimately, factors that significantly hinder efficiency include workup and purification, which require time and generate waste. Thus, the development of cascade and one-pot reactions provides ideal solutions that address this challenge. Within this paradigm, there is room for further increase in efficiency through the development of multimetal-catalyzed processes.[1] While chemists have yet to achieve Nature's capacity to have multiple catalysts operate within the same "vessel", the development of multimetal-catalyzed cascade reactions can afford highly modular and divergent syntheses.

(1) For selected examples of the use of two transition-metal catalysts in a domino transformation, see: (a) Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2372–2375. (b) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220–10221. (c) Komon, Z. J. A.; Diamond, G. M.; Leclerc, M. K.; Murphy, V.; Okazaki, M.; Bazan, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 15280–15285. (d) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607–1610. (e) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459–462. (f) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2004**, *126*, 16066–16072. (g) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312*, 257–261. (h) Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405–408. (i) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124–3125. (j) Shi, Y.; Roth, K. E.; Ramgren, D. D.; Blum, S. D. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023. (k) Takahashi, K.; Yamashita, M.; Ichihara, T.; Nakano, K.; Nozaki, K. *Angew. Chem.* **2010**, *122*, 4590–4592. *Angew. Chem., Int. Ed.* **2010**, *49*, 4488–4490. For selected examples of multimetallic cooperative catalysis, see: (l) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309–3310. (m) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664. (n) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345–347. (o) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674–3675. (p) Trost, B. M.; Luan, X. *J. Am. Chem. Soc.* **2011**, *133*, 1706–1709.

(2) Panteleev, J.; Zhang, L.; Lautens, M. *Angew. Chem.* **2011**, *123*, 9255–9258. *Angew. Chem., Int. Ed.* **2011**, *50*, 9089–9092.

(3) (a) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893–4902. (b) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397–3408. (c) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, UK, 1996; p 167. (d) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, 111943–1945. (e) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701–5704. (f) Turner, K. L.; Baker, T. M.; Islam, S.; Procter, D. J.; Stefaniak, M. *Org. Lett.* **2006**, *8*, 329–332. (g) Harmata, M.; Hong, X. *Org. Lett.* **2007**, *9*, 2701–2704.

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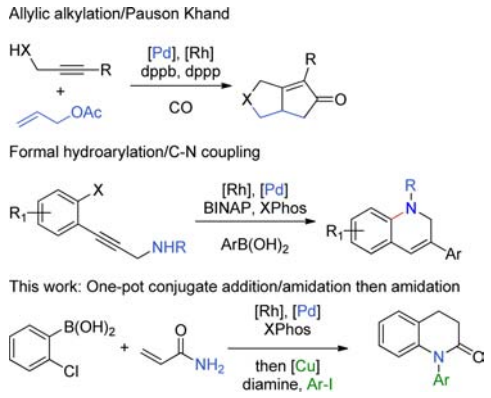


Figure 1. Developments in Rh/Pd dual catalysis.

Due to the highly versatile and orthogonal catalytic reactivity of rhodium and palladium,[2] we decided to apply the Rh/Pd system in a new conjugate addition/amidation catalytic multimetal method. We further expanded the modularity of this method with a subsequent Cu-catalyzed amidation that exhibited highly complementary reactivity (Figure 1). We could access quinolinones, which are ubiquitous scaffolds of drugs and natural products that possess potent biological properties (Figure 2).[3]

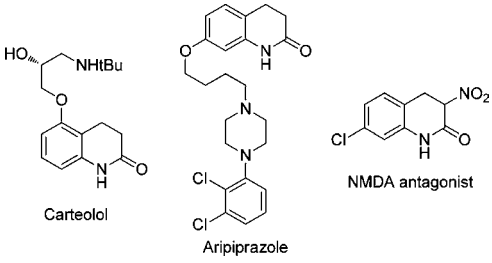


Figure 2. Drugs containing the 3,4-dihydroquinolinone scaffold.

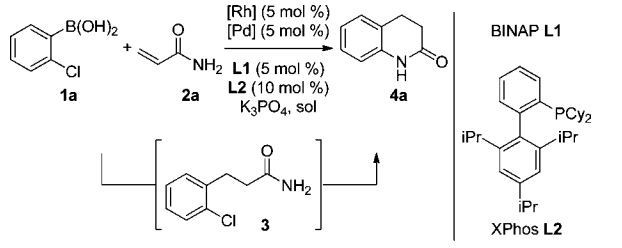
We began our study with the optimization of Rh-catalyzed conjugate addition of *o*-chloroarylboronic acid **1a** onto acrylamide **2a** (Table 1).[4] In general, the presence of an ortho substituent had a negative impact on the reaction but following optimization, a conjugate addition product **3**, employing catalytic amounts of $[Rh(cod)OH]_2$ and BINAP **L1** with dioxane/MeOH as solvent (entry 1) was found to afford the desired product in good yields. We then tested the compatibility of the conjugate addition with conditions that are typically employed in Pd-catalyzed amidation reactions.[5,6]

(4) For reviews on Rh-catalyzed conjugate addition, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093–2105. (c) Berthon, G.; Hayashi, T. Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley: Weinheim, 2010; p 1−70. For selected examples of conjugate addition onto amides, see: (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951–5955. (e) Frost, C. G.; Penrose, S. D.; Gleave, R. *Org. Biomol. Chem.* **2008**, *6*, 4340–4347.

We obtained excellent yields using K_3PO_4, *t*-BuOH, and *tert*-amyl alcohol (entries 2 and 3).

We next focused our attention on the development of Pd-catalyzed intramolecular amidation. The Pd-catalyzed amidation of aryl chlorides is a challenging reaction, but we were able to realize the reaction employing $Pd(OAc)_2$ and XPhos **L2** in the presence of K_3PO_4 and *t*-BuOH (entry 4).[6] We tested the compatibility of both metal-catalyzed reactions in one synthetic operation and were pleased with an initial conversion to **3** and **4a** in a yield of 49 and 35%, respectively (entry 5). Elevating the reaction temperature to 110 °C gave a smooth reaction to afford the desired dihydroquinolinone **4a** in 74% yield (entry 6). We opted for the use of *t*-am-OH as solvent due to its ease of handling. Further improvements in yield were achieved by switching the Pd-catalyst to $[Pd(allyl)Cl]_2$ (entry 7). We also observed a benefit by omitting BINAP (entry 8). Consequently, no catalyst premixing was required in the reaction setup, which significantly improved the operational practicality of the reaction. Lowering the amount of boronic acid to just 1.05 equiv not only improved the efficiency of the conjugate addition but also the subsequent step. This effect probably resulted from diminished protodeborolation to form chlorobenzene, a possible inhibitory byproduct for the Pd-catalyzed reaction. Finally, the use of a more cost-effective catalyst, $[Rh(cod)Cl]_2$, provided favorable reactivity (entry 9).

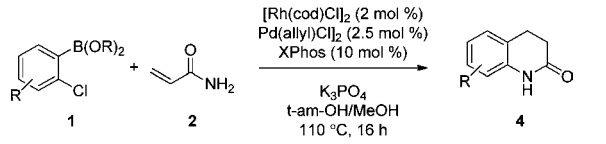
Table 1. Optimization of Reaction Conditions[a]

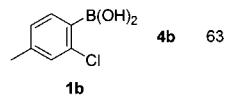
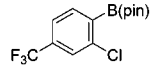
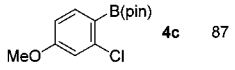
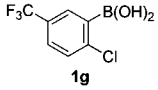
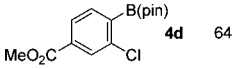
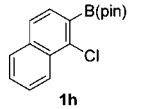
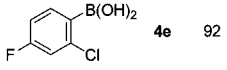
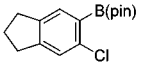
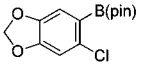


entry	[Rh]/**L1**	[Pd]/**L2**	sol/MeOH (10:1)	*t* (°C)	% yield **3a**/**4a**
1[b]	$[Rh(cod)OH]_2$	–	Dioxane	100	84/–
2	$[Rh(cod)OH]_2$	–	*t*-BuOH	100	89/–
3	$[Rh(cod)OH]_2$	–	*t*-am-OH	100	92/–
4[c]	–	$[Pd(OAc)_2]$	*t*-BuOH	100	–/99
5[d]	$[Rh(cod)OH]_2$	$[Pd(OAc)_2]$	*t*-BuOH	110	49/35
6	$[Rh(cod)OH]_2$	$[Pd(OAc)_2]$	*t*-BuOH	110	–/74
7	$[Rh(cod)OH]_2$	$[Pd(allyl)Cl_2]$	*t*-am-OH	110	–/73
8[e]	$[Rh(cod)OH]_2$ no **L1**	$[Pd(allyl)Cl_2]$	*t*-am-OH	110	–/76
9[e,f]	$[Rh(cod)Cl]_2$ no **L1**	$[Pd(allyl)Cl_2]$	*t*-am-OH	110	–/89 (87)

[a] Yields were determined by ^{1}H NMR spectroscopy. [Rh] and **L1** were premixed separately from [Pd] and **L2**, each in 1 mL of solvent for 15 min. The mixtures were transferred to a vial containing **1a** (1.5 equiv), **2a** (0.4 mmol), base (2.2 equiv) under argon atmosphere. The vial was stirred at rt for 15 min, sealed, and heated at the described temperature for 16 h. [b] K_2CO_3 was used instead of K_3PO_4. [c] Reaction conducted with **3** as substrate. [d] No MeOH as cosolvent. [e] No catalyst premixing; 1.05 equiv **1a**. [f] Isolated yield in parentheses. X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, *t*-am-OH = 2-Methyl-2-butanol (*tert*-amyl alcohol).

Table 2. Reaction Scope of Rh/Pd Conjugate Addition/Amidation[a]



entry	1	4	% yield	entry	1	4	% yield
1		**4b**	63	5		**4f**	78
2		**4c**	87	6		**4g**	96
3		**4d**	64	7		**4h**	80
4		**4e**	92	8		**4i**	53
				9		**4j**	54

[a] Reaction conducted at 0.4 mmol scale. See Supporting Information for detailed procedures. To a vial under argon atmosphere was added [Rh], [Pd], XPhos, **2a**, arylboronic acid (1.05 equiv), K_3PO_4 (2.2 equiv), followed by 2.2 mL of *t*-am-OH/MeOH (10:1). The vial was sealed, stirred at rt for 5 min, and heated at 110 °C for 16 h.

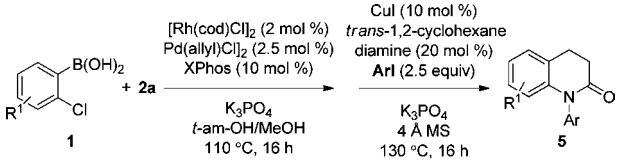
We next examined the scope of the $(MC)^2R$ (Table 2). Good reactivity was observed with pinacol protected boronic esters and these boronates can be accessed reliably and easily from phenols.[7] Good to high yields were observed with a variety of substituted boronic esters. The reaction tolerated substituents at various positions on the aryl ring. While electron-poor aryl groups afforded the highest yields, electron neutral aryl groups gave modest yields. Employing functionalized aryl boronates such as **1h** to **1j**, tricyclic lactams can be accessed (entries 7–9).

We sought to achieve the goal of conducting additional metal-catalyzed reactions in the same vessel without any workup/purification stages. Doing so would further add a level of efficiency. Thus, we attempted to perform a Cu-catalyzed arylation of the secondary lactam[8] immediately after Rh/Pd-catalysis. Following optimization, we could perform the Cu-catalysis in the same reaction solvent with CuI, a diamine ligand, an aryl iodide, molecular sieves, and the same base at an elevated temperature. Control studies on this step indicated the necessity of Cu, since Pd did not promote the reaction.

The Cu-catalyzed amidation (Table 3) offers highly complementary reactivity toward the Pd-catalyzed reaction. Iodoanilines and iodohalobenzenes (entries 6–8) can be used even in the presence of Pd and the desired reactivity for Cu catalysis was observed. Products over three catalytic cycles can be accessed in good to high yields.

Upon examination of substitutions on the acrylamide acceptor, the reaction seemed to be limited due to the Rh-catalyzed step. We observed a complex mixture once the acrylamide was *N*-alkyl or aryl substituted (Figure 3, eq 1). In addition, β-substituted acrylamides exhibited no reactivity (Figure 3, eq 2). Whereas arylboronic acids lacking ortho-halo substitution reacted smoothly with the aforementioned acrylamides,[4d] the *o*-chloro moiety was responsible for the lack of reactivity. Indeed, reports of conjugate

Table 3. Two-Step One-Pot $(MC)^2R$[a]



entry	R^1	Ar	5	% yield
1	H, **1a**	Ph	**5a**	80
2		4-Me-C_6H_4	**5b**	75
3		3-Me-C_6H_4	**5c**	74
4		4-MeO-C_6H_4	**5d**	71
5		3-CF_3–C_6H_4	**5e**	60
6		3-NH_2–C_6H_4	**5f**	77
7		4–Br-C_6H_4	**5g**	53
8		3,4-$(Cl)_2$-C_6H_3	**5h**	62
9	3-Me, **1b**	Ph	**5i**	57
10	**1b**	4-MeO-C_6H_4	**5j**	54
11	3-OMe, **1c**	Ph	**5k**	47
12	3-F, **1e**	Ph	**5l**	59
13	5-CF_3, **1g**	Ph	**5m**	58

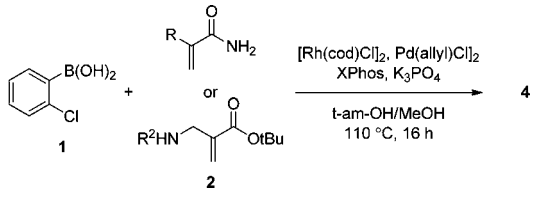
[a] See Supporting Information for detailed reaction procedures. Reaction conducted on 0.4 mmol scale.

(5) For reviews on C–N coupling, see: (a) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075. (b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. For selected examples of amidation of aryl chlorides, see: (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580. (d) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351–1354. (e) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207–2210. (f) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433–2435. (g) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371–1375. (h) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411–1414. Examples of the intramolecular amidation of aryl chlorides: (i) Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *7*, 863–866. (j) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311–3314.

(6) For the use of XPhos and similar bulky biaryl phosphines in amination of aryl chlorides, see: (a) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem.* **2006**, *118*, 6673–6677. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527. (b) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980. (d) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508. (e) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576–6583.

(7) For the preparation of ortho-chloroboronates, see: Barluenga, J.; Jiménez-Aquin, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031.

Table 4. Reaction Scope of Rh/Pd-Catalysis with Respect to α-Substituted Acrylamides/Acrylates[a]



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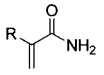
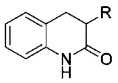
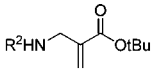
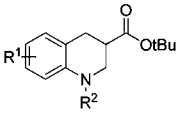
1	1a			
		R = Me, **2b** R = Ph, **2c**	R = Me, **4k** R = Ph, **4l**	57 21[b]
2[c]	1a or 1f			
		R^2 = Ph, **2d** R^2 = Ts, **2e**	R^1 = H, R^2 = Ph, **4m** R^1 = H, R^2 = Ts, **4n** R^1 = 4-CF_3, R^2 = Ts, **4o**	77[d] 69 71

[a] See Supporting Information and Table 2 for reaction procedures. Reaction conducted on a 0.2–0.4 mmol scale. [b] Performed with stepwise addition of $[Pd(allyl)Cl]_2$/XPhos after completion of Rh-catalyzed step. [c] Reaction performed with dioxane/MeOH as solvent. [d] RuPhos was used instead of XPhos.

additions of ortho-substituted arylboronic acids to acyclic α,β-unsaturated Michael acceptors are rare.[9] Even more scarce are reports on the ortho-halo-substituted arylboronic acids.[10]

However, we did identify a number of α-alkyl-substituted acrylamides and acrylates that displayed useful reactivity (Table 4). While methacrylamide (**2b**) provided the desired quinolinone (entry 1), larger α-alkyl substituents were less reactive in the Rh-catalyzed step. α-Phenyl acrylamide (**2c**) gave smooth conversion in the conjugate addition. The poor reactivity of the amidation step was the main obstacle, even with the use of a sequential catalyst/ligand addition protocol. Due to the attenuated reactivity

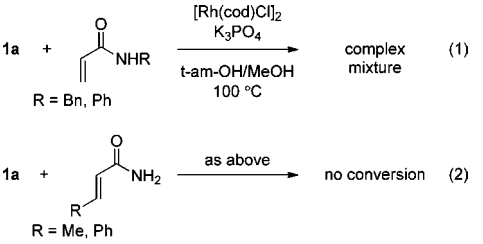


Figure 3. Reactivity of Rh-catalyzed conjugate addition of *o*-chloro phenylboronic acid onto substituted acrylamides.

of the aforementioned acrylamides, we investigated an alternative approach with acrylates bearing an α-methyl amino group (**2d** and **2e**). The more electrophilic acrylates facilitated the conjugate addition while the amino group can efficiently cyclize after the conjugate addition. This annulation strategy provided access to tetrahydroquinolines **4m**–**o** in good yields.

In summary, we have developed an efficient Rh/Pd conjugate addition/amidation sequence useful in the synthesis of dihydroquinolinones. We have also developed a one-pot triple metal catalyzed reaction. The use of ortho-halo arylboronates and acrylamides provides an annulation strategy which also can be applied to substituted acrylates to access tetrahydroquinolines. Combining compatible and complementary reactivity of metals should further highlight the potential, operational practicality, and efficiency of $(MC)^2R$.

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Supporting Information Available. Detailed experimental procedures and full compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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